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Title: Clinical effectiveness of elemental nutrition for the maintenance of remission in Crohn's disease: a systematic review and meta-analysis

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Paul Sutcliffe (Associate Professor) coordinated the report. Alexander Tsertsvadze (Senior Research Fellow), Tara Gurung (Research Fellow) and Paul Sutcliffe conducted the systematic review, this included: screening and retrieving papers, assessing against the inclusion criteria, appraising the quality of papers and abstracting data from papers for synthesis. Rachel Court (Information specialist) developed the search strategy and undertook searches. Aileen Clarke (Professor) wrote sections of the abstract, executive summary and discussion and provided comments throughout. All authors were involved in writing the draft and final versions of the report.

ABSTRACT

Background: Although enteral nutrition has been shown to be a viable treatment option for the management of active Crohn's Disease (CD), the evidence regarding its clinical benefits compared to standard treatments (e.g., steroids) for maintaining remission in patients with CD has been inconsistent. If enteral nutrition was to be effective, the use of drugs such as steroids and immunosuppressive drugs could be reduced, thereby reducing the likelihood of adverse events associated with these medications.

Objectives: This systematic review aimed to assess the effectiveness and cost-effectiveness of elemental nutrition (a type of enteral nutrition) for maintenance of remission in patients with CD.

Methods: Electronic searches of major databases (e.g., MEDLINE, EMBASE, CDSR), not limited by study design, language, or publication date were carried out. Websites for relevant organisations and references of included studies were checked. Randomised and non-randomised experimental controlled trials (RCTs and non-RCTs) reporting clinical effectiveness and/or cost-effectiveness of elemental nutrition in the maintenance of remission in patients with CD were eligible. Study selection, data extraction, and risk of bias assessment were performed independently. Risk ratios (RRs) and mean differences (MDs) were pooled using a random-effects model. Heterogeneity was assessed via forest plots, Cochran's Q and the I^2 statistics. Overall quality of evidence for each outcome was rated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Results: Twelve of 36 potentially relevant papers were included in the review (representing three RCTs and five non-RCTs). RCTs indicated a significant benefit of elemental nutrition vs. no intervention (an unrestricted diet) in maintaining remission at 24 months (one RCT; RR=2.06, 95% CI: 1.00, 4.43; very low grade evidence) and preventing relapse at 12-24 months post-baseline (two RCTs; pooled RR=0.57, 95% CI: 0.38, 0.84; high grade evidence). Similarly, three non-RCTs showed significant benefits of elemental nutrition over no intervention in maintaining remission at 12-48 months and preventing relapse at 12 months post-baseline (MD=1.20 months, 95% CI: 0.35, 2.04). Incidence of mucosal healing between intervention and control groups was not significantly different (RR=2.70, 95% CI: 0.62, 11.72). Adherence was significantly worse for an elemental compared to polymeric nutrition (RR=0.68, 95% CI: 0.50, 0.92). When compared to other active treatments (medications, polymeric nutrition, or a combination), elemental nutrition yielded non-significant results

with wide 95% CIs, rendering these results inconclusive. Complications and adverse events were too sparse to allow meaningful comparisons. None of the studies reported cost-effectiveness of elemental nutrition.

Limitations: The findings warrant cautious interpretation given the limitations of the evidence in methodological quality (small samples, short follow-up) and the risk of bias in individual studies (lack of blinding, confounding). Due to scarcity of data, no subgroup or sensitivity analysis was performed.

Conclusions: Limited evidence indicates potential benefits of elemental nutrition against no intervention in the maintenance of remission and prevention of relapse in adult patients with CD. There was lack or insufficient evidence on adverse events and complications. Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

PLAIN ENGLISH SUMMARY

We conducted a systematic review of eight prospective controlled experimental trials which examined the effectiveness of elemental nutrition for the maintenance of remission in patients with Crohn's disease (CD). Based on the limited amount of evidence, elemental nutrition was more beneficial than an unrestricted diet for the maintenance of remission and prevention of relapse in the short-term. Evidence comparing the benefits of elemental nutrition to other treatment options (standard medication, polymeric nutrition) for maintaining remission was uncertain, and therefore, inconclusive. There was insufficient information on adverse events and complications. This review identified methodological shortcomings of individual studies (small samples, short follow-up, bias) and gaps in evidence (no cost-effectiveness studies of elemental nutrition for maintenance of remission; no studies of elemental nutrition in children or young adults in remission). Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

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GLOSSARY

Enteral nutrition

A method of delivering nourishment through a tube placed in the nose (nasogastric or nasoenteral tube), the stomach (gastrostomy or percutaneous endoscopic gastrostomy tube), or the small intestine (jejunostomy or percutaneous endoscopic jejunostomy tube). Enteral nutrition varies in the protein and fat content and can be classified as elemental, semi-elemental, polymeric or specialised.

Elemental nutrition

Elemental nutrition is a liquid monomeric amino-based formula, which contains individual amino acids, glucose polymers, and is low in fat with about 2% to 3% of calories derived from long chain triglycerides (LCT). Elemental nutrition formula does not contain antigens.

Semi-elemental nutrition

Semi-elemental nutrition is liquid oligopeptide formula that contains peptides of various chain lengths, simple sugars, glucose polymers or starch and fat, mainly as medium chain triglycerides (MCT).

Polymeric nutrition

Polymeric nutrition is a liquid whole-protein based formula that contains intact proteins (sources: milk, meat, egg, soy), complex carbohydrates and mainly LCTs.

Specialised nutrition

Specialised nutrition is liquid formula that contains biologically active substances or nutrients such as glutamine, arginine, nucleotides or essential fatty acids.

Parenteral nutrition and total parenteral nutrition

Parenteral nutrition involves feeding via the blood stream intravenously, total parenteral nutrition means feeding solely via the intravenous route.

LIST OF ABBREVIATIONS

AST	Aspartate transaminase
ASA	Amino-salicylic acid
BMI	Body Mass Index
CD	Crohn’s disease
CDAI	Crohn’s disease activity index
CDSR	Cochrane Database of Systematic Reviews
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CICRA	Crohn's in Childhood Research Association
CI	Confidence interval
CRP	C - reactive protein
CCTs	Controlled clinical trials
DARE	Database of Abstracts of Reviews of Effects
ED	Elemental Diet
EMBASE	Excerpta Medica Database
EEN	Exclusive enteral nutrition
ESR	Erythrocyte sedimentation rate
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HR	Hazard ratio
HQOL	Health-related quality of life
IBD	Inflammatory bowel disease
IOIBD	International Organization for the Study of Inflammatory Bowel Disease
ICER	Incremental cost-effectiveness ratio
LCT	Long chain triglycerides
MCT	Medium chain triglycerides
MD	Mean difference
MP	Mercaptopurine
MEDLINE	Medical Literature Analysis and Retrieval System Online
nRCT	Non randomised controlled trial
NACC	National Association for Colitis and Crohn's Disease
NA	Not applicable
NG	Nasogastric
NICE	National Institute for Health and Clinical Excellence

NI	No intervention
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NS	Not significant
NR	Not reported
OR	Odd ratio
PEN	Partial Enteral Nutrition
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOL	Quality of life
QALYs	Quality-adjusted life-years
RR	Risk ratio (relative risk)
RCT	Randomised controlled trial
ROB	Risk of bias
SD	Standard deviation
SE	Standard error
SS	Statistically significant
SROB	Summary risk of bias
TNF	Tumor necrosis factor
UK	United Kingdom
UKCRN	UK Clinical Research Network
WHO	World Health Organisation
WHO ICTRP	WHO International Clinical Trials Registry Platform

EXECUTIVE SUMMARY

Background

Crohn's disease (CD) is a relapsing-remitting condition which causes chronic inflammation of the gastrointestinal tract. Frequent symptoms of CD include malnutrition, abdominal pain, diarrhoea, and weight loss. The objective of CD management is to induce and maintain remission of disease by controlling inflammation, reducing clinical symptoms, and preventing complications. The management of children with CD involves additional goals to promote normal growth and pubertal development. The choice of therapy depends on the extent of inflammation, the disease severity, and complications.

None of the currently available therapeutic options including medical (e.g., corticosteroids, biologics, antibiotics), surgical (e.g., bowel resection), and nutritional (e.g., enteral/parenteral feeding, restricted diet) leads to complete cure of CD. Although corticosteroids are the most widely used drugs for the treatment of active CD and their use has been shown to be associated with short-term remission, they are also associated with steroid dependency, impairment in growth, and risk of infection. Tumour necrosis factor inhibitors are also used but there are safety concerns with their long-term use.

Recently, enteral nutrition has been shown to be a viable treatment option in the management of active forms of CD. But evidence regarding the efficacy of an enteral nutrition relative to standard treatment (i.e., steroids) has been inconsistent. For example, one meta-analysis showed that enteral nutrition was at least as effective as steroids in inducing remission in children and young adults with active CD. In contrast, a more recent meta-analysis indicated that enteral nutrition was less beneficial compared to steroids in inducing remission in adults with active CD. In Japan, enteral nutrition is recommended as the first-line treatment in the management of active CD.

Evidence for the efficacy of different types of enteral nutrition (i.e., elemental, semi-elemental, polymeric) in maintaining remission in CD has been insufficient and is less clear. Most of the comparative evidence on the maintenance of remission rests on a few retrospective observational cohort studies and prospective non-randomised controlled trials (non-RCTs). If enteral nutrition proves to be as effective as conventional medications, its use might minimize or replace the use of conventional drugs (e.g., steroids).

Objectives

This review aimed to evaluate clinical effectiveness and cost-effectiveness of elemental nutrition (a type of enteral nutrition) for the maintenance of remission in CD. The specific aims of this review were to explore:

- The clinical effectiveness and cost-effectiveness of elemental nutrition compared to other interventions (e.g., placebo, unrestricted diet, standard drug treatment, or other types of enteral nutrition such as polymeric and semi-elemental) for maintaining remission in patients with quiescent CD.
- Whether the treatment effect of elemental nutrition on the maintenance of remission varies across groups defined by dose/duration of elemental nutrition, sex (males, females), age (adults, adolescents, and children), and type of induction therapy (medically-, nutritionally-, surgically-induced).
- Additional outcomes for patients with CD: adherence to elemental nutrition, CD activity index (CDAI), incidence of mucosal healing, quality of life (QOL), adverse events, gain in body weight (or body mass index [BMI]), growth, and pubertal development.

Methods

Search strategy and data sources

Electronic searches were carried out in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE (via OVID); CDSR, CENTRAL, DARE, NHS EED, HTA database (via the Cochrane Library); Science Citation Index and Conference Proceedings (via Web of Knowledge); WHO ICTRP; UKCRN Study Portfolio. The searches were not limited by study design, language, or publication date. Websites for relevant organisations as well as references of included studies were checked for relevant studies. All the retrieved records were collected and then de-duped using a specialized database.

Study eligibility criteria

English publications of RCTs and non-RCTs comparing clinical effectiveness and/or cost-effectiveness of elemental nutrition to no intervention (restricted/unrestricted diet) or other types of treatment (e.g., placebo, semi-elemental/polymeric nutrition, standard drug therapy) in patients with CD in remission at baseline were eligible for inclusion. Reviews, meta-analyses, observational cohort studies, case-reports, case-series, editorials, or comments were excluded.

Outcomes of interest

Primary review outcomes were maintenance of remission (% patients maintaining remission, cumulative probability of remission, and duration of remission), development of relapse (% patients developing relapse, time to relapse), and incidence of mucosal healing (% patients with endoscopic mucosal healing). Secondary outcomes were adherence to elemental nutrition, need for surgery, withdrawals from steroids, CDAI score, QOL, gain in body weight or BMI, pubertal development, adverse events, and complications.

Study selection and data extraction

Two independent reviewers used a pre-piloted form to screen the identified records for title/abstract. Afterwards, full text reports of all potentially relevant abstracts were retrieved and examined independently. Disagreements were resolved via discussions and consensus agreement.

Two reviewers using a pre-piloted form independently extracted relevant data on study (e.g., author, country, design, sample size), participant (e.g., age, sex, type of induction therapy), intervention (e.g., type, mode/dose of administration, concomitant diet or medications), and outcome characteristics (e.g., scale of measurement, assessment timing, definition of CD relapse). The extracted data were cross-checked by second reviewer and any disagreements were resolved by discussion.

Risk of bias assessment

Two reviewers independently assessed risk of bias of individual studies. We used the Cochrane Collaboration Risk of Bias (ROB) tool to assess RCTs which rates risk of bias (high, low, and unclear) across selection, performance, detection, attrition, and reporting domains. Non-RCTs were assessed using a modified Cochrane ROB tool in which the domain of selection bias was evaluated in regards to baseline between-group imbalance for important prognostic factors. Disagreements on extractions were resolved by a third reviewer through discussion.

The quality of economic analyses of the included studies was planned to be assessed using the Drummond 10-item checklist.

Data synthesis and overall quality of evidence

Study, treatment, population, and outcome characteristics were summarised in text and summary tables. The data on effectiveness of elemental nutrition for each outcome of interest were compared qualitatively and quantitatively in text and summary tables. Results for each outcome were stratified

by a comparison of elemental nutrition to no intervention (i.e., restricted/unrestricted diet), drug alone, combination of elemental nutrition and drug, and other types of enteral nutrition.

The decision to pool data was based on a degree of similarity with respect to methodological and clinical characteristics of studies. Post-treatment mean differences for continuous and risk ratios for binary measures were planned to be pooled using a DerSimonian and Laird random-effects model. The degree of heterogeneity was determined through inspection of the forest plots, Cochran's Q and the I^2 statistics. The heterogeneity was judged according to pre-determined levels of statistical significance (Chi^2-based $p<0.10$ and/or $I^2>50\%$). Study-level clinical and methodological sources of heterogeneity was planned to be explored through a priori defined subgroup (i.e. age, sex, induction therapy) and sensitivity analysis. Publication bias was planned to be assessed through visual inspection of funnel plots for asymmetry and use of linear regression tests.

Results were rendered inconclusive in cases of missing/partially reported data (undetermined effect measures, 95% confidence intervals) or statistically non-significant effect estimates with great uncertainty (i.e., sufficiently wide intervals that include moderate to large effect size treatment effects in both directions compatible to either benefit or harm of elemental nutrition).

The overall quality of evidence (high, moderate, low, very low grade) for pre-selected gradable outcomes (e.g., maintenance of remission, risk of relapse) was assessed using an approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org).

Results

A total of 630 records were identified and screened, of which 594 were excluded at title/abstract level. Of the remaining 36 records screened at full-text level, 12 were included in the review (representing three RCTs and five non-RCTs).

Out of eight studies, six were conducted in Japan and two in the UK. The sample size ranged from 33 to 95 participants. The mean age ranged from 22 to 44 years and length of follow-up from 12 to 48 months. Type of induction therapy in most studies was medical (standard drugs, enteral or parenteral nutrition). Elemental nutrition was given in addition to unrestricted/restricted diet through tube infusion and/or oral intake. Participants in the control groups received either unrestricted diet (no intervention), standard drug (e.g., 6-MP, infliximab, prednisolone) or polymeric nutrition.

RCTs indicated a significant benefit of elemental nutrition vs. no intervention (unrestricted diet) in maintaining remission after 24 months of follow-up (one RCT; RR=2.06, 95% CI: 1.00, 4.43; very low grade evidence) and preventing relapse at 12-24 months of follow-up (two RCTs; pooled RR=0.57, 95% CI: 0.38, 0.84; high grade evidence). The 6-12 month maintenance rate was not significantly different (RR=1.37, 95% CI: 0.86, 2.17; very low grade evidence; inconclusive result due to wide 95% CIs).

Similarly, three non-RCTs showed significant benefits of elemental nutrition over no intervention (unrestricted diet) in maintaining remission and preventing the occurrence of relapse at 12 months. In one non-RCT, the use of elemental nutrition was associated with a significantly longer time to relapse compared to no intervention (MD=1.20, 95% CI: 0.35, 2.04). Incidence of mucosal healing between elemental nutrition vs. no intervention (unrestricted diet) groups at 12 months was not significantly different (inconclusive results; RR=2.70, 95% CI: 0.62, 11.72).

There was a significantly worse adherence rate to elemental nutrition compared to an unrestricted diet or polymeric nutrition (RR=0.68, 95% CI: 0.50, 0.92).

In general, effects of elemental nutrition vs. active treatments (medications, polymeric nutrition, or combination) yielded statistically non-significant results across outcomes with wide 95% CIs including moderate to large treatment effects in both directions and compatible with both benefit or harm of elemental nutrition (inconclusive results). Data on complications and adverse events were too sparse (e.g., zero events, low counts) to derive effect estimates and 95% CIs or to permit any meaningful comparison between the treatments.

There was no evidence for children with CD. Likewise, none of the studies reported cost-effectiveness of elemental nutrition.

Due to scarcity of data, no subgroup or sensitivity analysis could be performed.

Discussion

Evidence from two RCTs and three non-RCTs demonstrated short-term benefits of elemental nutrition for the maintenance of remission and prevention of relapse compared to no treatment (i.e., unrestricted diet). Adherence rates were lower in the elemental vs. no intervention or polymeric nutrition groups. This finding may be explained by the inconvenience of nasogastric feeding, poor palatability, and/or higher cost of elemental nutrition compared to an unrestricted diet or polymeric

nutrition. One RCT showed no difference in QOL between elemental nutrition and no intervention (unrestricted diet).

Generally, differences across outcomes between elemental nutrition and active treatments (i.e., medications, polymeric nutrition, or combination) were not statistically significant. These results should not be interpreted as the treatments being equivalent (or the absence of effect of elemental nutrition). The associated 95% CIs were wide and uninformative suggesting both benefit and harm of elemental nutrition. Therefore, these results are inconclusive.

The data on complications and adverse events was too sparse to permit any meaningful comparison between the treatments. It is unclear whether insufficient evidence on adverse events and complications is due to the absence or rarity of these events or it is simply due to underreporting of such events.

The review findings warrant cautious interpretation given the limitations of evidence in terms of methodological quality (small samples, short follow-up) and risk of bias in individual trials (lack of blinding, confounding). Non-RCTs in particular may have been biased because of the possibility of uneven distribution of known (e.g., location of the lesion, disease duration) or unknown prognostic factors between groups. In some non-randomised trials, patients with 'good compliance' were assigned to elemental nutrition and those with 'poor compliance' to the control treatment. It is hard to predict the direction of bias (if any), if good and poor compliers differed systematically.

Future research using long-term large RCTs would fill-in gaps in evidence (e.g., studies in young adolescents and children; effects of exclusive elemental nutrition; effects of elemental nutrition in subgroups) and improve reporting practices in relation to trial methodology and completeness of reported data for better interpretability of evidence. More research exploring better tasting elemental nutritional formulas to maximize the adherence rate to elemental nutrition is also warranted.

Conclusions

There is limited evidence indicating benefits of elemental nutrition in the maintenance of remission and prevention of relapse in adult patients with CD. There was lack or insufficient evidence on adverse events and complications. Methodological shortcomings of individual studies and gaps in evidence have been identified. Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

1 BACKGROUND

1.1 Description of health problem

1.1.1 Health problem

Crohn's disease (CD), a form of inflammatory bowel disease (IBD), is a chronic relapsing-remitting condition which causes chronic inflammation of the gastrointestinal tract. CD can affect any part of the digestive tract, from the mouth to the anus.[1] Usually, CD involves both the superficial and deep layers of the intestine.[2] CD may be characterized by location (terminal ileal, colonic, ileocolic, upper gastrointestinal) and/or pattern of disease (inflammatory, perforating, or stricturing).[3] The most frequently reported symptoms of CD include malnutrition, abdominal pain, diarrhoea, weight loss, fever, and rectal bleeding.

The disease can occur at any age from early childhood to late adulthood. However, it is more common among age group between 15 and 25 years. Male and female are affected equally.[4, 5] Around one third of people with CD are diagnosed before 21 years of age.

1.1.2 Aetiology of CD

The aetiology of CD is unknown. It is hypothesized that CD may result due to interactions amongst genetic, immunological and environmental factors.[6] Smoking and genetic predisposition are the two important factors thought to play a key role in the aetiology of CD.[7]

1.1.3 Clinical features of CD

The clinical course of CD is characterised by exacerbations and remission.[3] The clinical presentation depends on the part of the affected intestine and varies from mild to severe malnutrition, abdominal pain, diarrhoea, weight loss, fever, and rectal bleeding.[5, 8] The symptom pattern in children is different to that of adults, and is instead characterized by anaemia, fever, growth failure and/or delayed puberty.[8]

1.1.4 Diagnosis of CD

Initial assessment of patients with suspected CD includes history taking, physical findings and routine blood and stool tests. Further examinations including plain abdominal radiography, colonoscopy, flexible sigmoidoscopy, endoscopy or barium x-ray are also performed. The diagnosis of CD depends upon the pathological findings of focal, asymmetric, transmural, or often granulomatous inflammation. Upper or lower gastrointestinal endoscopy should be performed to confirm the diagnosis of CD and assess disease location.[8-10]

1.1.5 Prognosis of CD

CD is considered a serious disease which needs extensive and long-term treatment with continuous monitoring.[11] Quality of life is reduced for CD patients during relapse but patients with few relapses or with continuous mild symptoms manage to lead a normal life.

CD patients are affected not only physically, but also mentally (for example with depression) impacting on both their personal and professional lives. Patients with CD take more time off work and may change their time schedules at work as a direct result of their disease.[12-14]

As the disease progresses, patients develop complications such as strictures, perforation, and/or fistula formation, from 50% to 80% of whom will eventually require surgical interventions.[7]

The mortality rate amongst patients diagnosed with CD has been shown to be greater for those diagnosed at an earlier age. For example, a study by Canavan et al. reported a standardised mortality ratio (SMR) among CD patients and showed that younger patient had a worse prognosis compared to older patients (overall SMR=1.29, 95% CI: 1.12, 1.45). The SMR for patients aged 10–19 years was 16.95 (95% CI: 14.99, 18.91) compared to an SMR of 0.92 (95% CI: 0.65, 1.19) for patients aged 75 years or older. Compared to the general population, mortality of patients with CD is also significantly higher in the first 3 years after diagnosis or for patients who have had the disease for 13 years or more. Actual cause of death could be anything directly related to the disease or as a consequence of the disease such as surgery, malnutrition, colorectal cancer, electrolytes imbalance or massive haemorrhage.[13, 14]

1.1.6 Epidemiology of CD

CD has become an important health threat in the West and industrialised countries.[15] The areas with the highest incidence rate are the United Kingdom (UK), North America, and northern Europe.[16] The annual incidence of CD in Europe and North America has been increasing over time and is estimated to be around 2 to 8 per 100,000 population. Similarly, the prevalence of the disease in the Western world has been estimated as approximately 60 per 100,000.[4]

In the UK, CD is one of the most common causes of gastrointestinal morbidity. In the North of England and Scotland, more recent estimates of the prevalence of CD indicate it to be between 145 and 157 per 100,000.[17] Scotland has a higher incidence rate compared to London and Wales. In the UK, there are currently at least 115,000 people with CD.[7]

Approximately 80% of CD patients will require surgery over their lifetime.[18] Between 1990 and 2000, the rate of hospital admissions rose from 7,648 to 8,834 in England (16% increase). The age standardised admission rate for CD increased from 15.5 to 17.6 per 100,000 (14% increase). The hospital admission rate (in 1999-2000) was higher in females than in males, with a female to male ratio of 1.5. According to age specific admission rates however the hospital admission rate was higher for the 25-34 age groups with a more equal distribution between males and females.[19]

1.1.7 Impact of CD

CD typically affects people during their economically productive adult life and many require life-long medical and surgical interventions over several decades. The financial burden due to the management of CD is very large.[20] Bassi et al (2004) reported a detailed micro-costing analysis of costs of illness for IBD in inner city patients for the UK National Health Services. Using hospital records, the authors identified and followed up 479 patients who had received some form of secondary care for IBD for up to 6 months. The mean six-month cost per patient for CD was found to be £1,652.00 (95% CI: 1,221, 2,239). Similarly, costs for ambulatory and hospitalisation groups were £516.00 (95% CI: 452, 618) and £6,923.00 (95% CI: 5415, 8919), respectively.[21]

1.1.8 Measurement of disease

The most widely used tool for characterising the activity (i.e., severity) of CD is the Crohn's Disease Activity Index (CDAI).[8] Patients with CDAI score < 150 are often classified as having a quiescent or non-active (i.e. in remission) form of disease. A CDAI score ≥ 150 is indicative of an active form of the disease.[22] CDAI is also used in conjunction with additional parameters/markers such as erythrocyte sedimentation rate (ESR) and C Reactive Protein (CRP).[23]

1.1.9 Current service provision

Management of CD

According to the current NICE guideline, the management of CD consists of smoking cessation, treatment with drugs, nutritional support, and surgery (in severe or chronic cases). The aim of treatment is mainly to reduce symptoms by inducing and maintaining remission so that quality of life improves.[7]

The treatment of CD can be categorised as non-surgical and surgical.

a) Non-surgical interventions include:

- Smoking cessation

- Pharmacological (Corticosteroids, biologics, aminosalicylates, immunosuppressants, tumour necrosis factor inhibitors, antibiotics)
- Nutritional (enteral feeding, restricted diet, parenteral feeding) alone or, as an adjuvant therapy

b) Endoscopic/surgical interventions (indicated for complications such as bowel obstruction, high grade dysplasia, abscess, internal fistulas, and cancer)

The treatment is chosen after considering a balance between individual response in terms of beneficial effects, treatment-related adverse events, and long term complications.[23, 24] Corticosteroids are most widely used for the management of active CD. However, their use is associated with high risk of relapse, low rates of mucosal healing, steroid dependency, and other adverse events (e.g., growth impairment in children, increased risk of infection). There have been safety concerns with long term use of other agents such as tumour necrosis factor (TNF) inhibitors.[1] A summary of the relevant national guidelines, including National Service Frameworks are provided in Table 1.

Table 1: Relevant national guidelines, including National Service Frameworks

NICE Guideline (NICE clinical guideline 152) 2012[7]

- First line therapy in children and young people to improve growth and development

BSG Guidelines 2011 (British Society of gastroenterology)[25]

- Usually used as an alternative therapy to corticosteroid for active CD
- 60 -80% effective on inducing remission for small and large bowel disease

ESPEN guideline 2006 (European Society for Clinical Nutrition and Metabolism)[26]

- First line induction therapy for children with CD
- Liquid diet only as sole therapy in adult when treatment with corticosteroid is not possible
- In case of persistent intestinal inflammation for patient with steroid dependent EN is used in the maintenance of remission

Inflammatory Bowel disease (IBD) Working Group of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition[3]

- First line induction therapy for small and large bowel disease
- To improve nutritional and growth status
- Both polymeric and elemental nutrition are of similar effect at inducing remission

1.2 Description of technology under assessment

1.2.1 Summary of intervention

Enteral nutrition has played an important but controversial role in the alleviation of malnutrition and control of disease activity in patients with active CD. Enteral nutrition formulas vary in the protein and fat content and are classified as elemental (amino-acid), semi-elemental (oligopeptide), polymeric (whole protein) or specialised diet.[27, 28] Enteral nutrition is a method of delivering nourishment through a tube placed in the nose (nasogastric or nasoenteral tube), the stomach (gastrostomy or percutaneous endoscopic gastrostomy tube), or the small intestine (jejunostomy or percutaneous endoscopic jejunostomy tube).

Elemental nutrition is a liquid formula that contains individual amino acids, glucose polymers, and is low in fat with approximately 2% to 3% of calories derived from long chain triglycerides (LCT). In many elemental products, medium chain triglycerides (MCT) are the main fat source, and are absorbed directly across the small intestinal mucosa into the portal vein in the absence of lipase or bile salts. Semi-elemental nutrition contains peptides of various chain lengths, simple sugars, glucose polymers or starch and fat. Polymeric nutrition contains intact proteins, complex carbohydrates and mainly LCTs. Specialised nutritional formulas contain biologically active substances or nutrients such as glutamine, arginine, nucleotides or essential fatty acids.[28, 29]

The mechanism of action of enteral nutrition on CD is not known. Several hypothesised mechanisms underlying the proposed benefits of enteral nutrition in CD include reduced gut activity, include reduction of antigenic load, nutritional effects, anti-inflammatory effects, or modulation of immune system and gastrointestinal flora.[30-33]

1.2.2 Types and route of administration

- As exclusive enteral nutrition (EEN): provided especially as a sole dietary source and a primary medical therapy to induce remission
- As partial enteral nutrition (PEN): given additionally to normal unrestricted/restricted diet, to improve nutritional status and /or to maintain remission

Both EEN and PEN may be administered either orally or with nasogastric (NG) tube.[34]

1.2.3 Enteral nutrition as induction therapy

There is some evidence of clinical benefit and long term safety of enteral nutrition in inducing remission in patients, especially children and young adults with active CD[35, 36] and in maintaining the

remission of quiescent CD.[30] For example, in Japan, enteral nutrition is recommended as the first-line treatment in the management of active CD.[33, 37] It has also been recommended as first line therapy in children and young adults with concerns about growth and side effects. Although enteral nutrition has been shown to be an effective and safe intervention for induction of remission in patients with active CD, withdrawal from enteral nutrition and resumption of normal diet would often be followed by reoccurrence of gastrointestinal symptoms and use of corticosteroids.[38] Evidence comparing clinical effectiveness of enteral nutrition to corticosteroids for the induction of remission has been inconsistent, with one meta-analysis showing no difference between the two,[36] and a more recent meta-analysis indicating a superiority of corticosteroids over enteral nutrition.[27]

1.2.4 Enteral nutrition as maintenance therapy

Evidence of the efficacy of different types of enteral nutrition (i.e., elemental, semi-elemental, polymeric) in maintaining remission in CD has been insufficient and less clear.[1, 3, 4, 15]

NICE recommends that enteral nutrition should not be used as maintenance therapy after surgery.[7] Moreover, use of enteral nutrition as maintenance therapy is challenging due to compliance issues.[1] Most evidence on the comparative clinical effectiveness of enteral nutrition in the maintenance of CD remission rests upon retrospective observational cohort studies and prospective non-randomised controlled experimental trials.[1, 3, 15]

2 DEFINITION OF THE DECISION PROBLEM

2.1 Decision problem

Crohn's disease (CD) is a chronic relapsing-remitting inflammatory disease affecting the gastrointestinal tract.[1] Currently, none of the available therapeutic options (e.g., medical, surgical, or nutritional) lead to complete cure of CD. The management of the disease usually involves the induction and then maintenance of remission of disease activity by controlling the extent of inflammatory process, correcting malnutrition, and reducing symptoms as well as the occurrence of complications.[23, 24] In children, the additional aim of the treatment is to promote healthy growth and development.

Enteral nutrition is one of the available treatment options in the management of CD and has been shown to be beneficial in inducing remission and improving nutritional status in adults and children diagnosed with active CD.[31, 37] There is less clarity of the role of enteral nutrition in maintaining remission in patients with quiescent CD.

If enteral nutrition is at least as effective as standard medical treatments, it could potentially replace or minimize the use of steroids and/or other pharmaceutical agents, thereby prevent the occurrence of adverse events, complications, steroid dependence, and growth retardation in both adults and children with CD.

The objective of this systematic review was to identify, appraise and evaluate the evidence on clinical effectiveness and cost-effectiveness of elemental nutrition for the maintenance of remission in CD.

2.2 Overall aims and objectives of assessment

- To evaluate the clinical effectiveness and cost-effectiveness of elemental nutrition administered alone or in combination with other interventions (e.g., diet, standard drug treatment) compared to other intervention(s) (e.g., placebo, diet, standard drug treatment) for maintaining remission in patients with CD.

- To compare the clinical effectiveness and cost-effectiveness of elemental nutrition with other types of enteral nutrition (semi-elemental, polymeric nutrition), duration, and dose in regards to maintaining remission and adherence.

- To explore subgroup effects of elemental nutrition on maintenance of remission (i.e., risk of relapse or recurrence). Specifically, to examine if the treatment effect of elemental nutrition varies across groups defined by sex (males, females), age (adults, adolescents, and children), and type of induction therapy (medically-, nutritionally-, surgically-induced).

- To evaluate additional outcomes for patients with CD such as adherence to elemental nutrition, CD activity index (CDAI), incidence of mucosal healing, quality of life, adverse events, gain in body weight (or BMI), growth, and pubertal development.

3 METHODS

The review protocol is provided in Appendix I and is registered on PROSPERO International prospective register of systematic reviews (CRD42013005134; available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013005134).

3.1 Search strategies

Using an iterative procedure an experienced librarian developed the search strategy with input from clinical advisors and previous systematic reviews.[37-39]

Comprehensive electronic searches were conducted to identify all references relating to elemental nutrition, maintenance of remission, and CD. Searches were undertaken in August 2013 in MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE (via OVID); CDSR, CENTRAL, DARE, NHS EED, HTA database (via the Cochrane Library); Science Citation Index and Conference Proceedings (via Web of Knowledge); WHO ICTRP; UKCRN Study Portfolio. The databases were searched from 1947 to August 2013; the actual data range for each of the databases searched depended on the coverage of the individual database. The electronic searches were not limited by study design, language, or publication date.

Citation searches of included studies were undertaken using the Web of Science citation search facility.

Two supplementary database searches using limits were undertaken. The first, combining CD with the concept of nutrition therapy and limited to systematic reviews or cost-effectiveness, aimed to capture any articles that included the assessment question as part of a broader systematic review or cost study. The second, combining CD with the concept of elemental nutrition and limited to relevant study types aimed to capture any articles that involved the current included population (see section 3.2) as part of a controlled clinical trial of both active CD and CD in remission.

Websites such as Crohn's and colitis UK (NACC);[5] Crohn's nutricia;[40] and Children with Crohn's and Colitis (CICRA)[41] were also checked.

In addition, experts in the field were contacted and references of included studies were also checked for potentially relevant studies.

All the retrieved records were collected in a specialised database. Duplicate records were identified and removed from the database.

Details of the electronic search strategies used for the review of the clinical effectiveness are given in Appendix II.

3.2 Study inclusion criteria

Type/language of publication:
English full text and abstracts (only if companion publications to full text included studies).

Study design:
RCTs and non-randomised controlled clinical trials.

Population:
Adults, young people, or children with CD in remission (inactive, quiescent CD) at the time of study baseline.

Main intervention:
Elemental nutrition alone via oral passage, nasal passage (naso-gastric tube, naso-jejunal tube, naso-duodenal tube), or direct passage via the abdomen (gastrostomy tube, jejunostomy tube).

Elemental nutrition in combination with other intervention(s) (e.g., standard drug therapy any other type of treatment).

Comparator:
Enteral nutrition (elemental, semi-elemental, or polymeric nutrition) alone, normal unrestricted/restricted diet alone (i.e., no intervention), standard drug therapy alone, any other intervention, or placebo.

Enteral nutrition (elemental, semi-elemental, or polymeric nutrition) in combination with other intervention(s) (e.g., standard drug therapy, any other intervention or placebo).

Standard drug therapy in combination with any other intervention, and/or placebo.

3.3 Study exclusion criteria

- Induction studies (patients with active CD at baseline) with or without follow up of remitted patients continuing to receive maintenance therapy
- Studies of parenteral (intravenous) nutrition
- Studies of ulcerative colitis
- Studies employing non-concurrent (e.g., historical) controls
- Studies with mixed patient populations (< 80% Crohn's disease)
- Studies comparing different formula/diets of elemental nutrition
- Reviews (systematic or non-systematic), meta-analyses, observational cohort studies, case-reports, case-series, editorials, abstracts, or comments

3.4 Outcomes of interest

Outcomes – clinical effectiveness:

Adult populations

- Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], and duration of remission) - primary outcome
- Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) – primary outcome
- Incidence of mucosal healing (n/N) – primary outcome
- Need for surgery (n/N)
- Withdrawal from steroids (n/N)
- Steroid dose tapering (n/N)
- CDAI score (mean endpoint or mean change from baseline)
- Health related quality of life (mean score: endpoint or mean change)
- Adverse events (n/N)
- Complications of CD (n/N)
- Gain in body weight or BMI (mean change in kg or kg/m^2)
- Adherence (n/N)

Younger populations (e.g., adolescents, paediatric)

- Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], and duration of remission) – primary outcome
- Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) – primary outcome
- Incidence of mucosal healing (n/N) – primary outcome
- Need for surgery (n/N)
- Withdrawal from steroids (n/N)
- Steroid dose tapering (n/N)
- CDAI score (mean endpoint score or mean change score from baseline)
- Health related quality of life (mean score: endpoint or mean change)
- Adverse events (n/N)
- Complications of CD (n/N)
- Gain in body weight or BMI (mean change in kg or kg/m^2)
- Adherence (n/N)
- Growth (mean change score/any growth measure from baseline)
- Pubertal development

Outcomes – cost-effectiveness:

- Costs (no efficacy measures: cost-minimisation analysis)
- Costs and efficacy measures - clinical and quality-adjusted life years (QALYs) (full economic analysis)
- Incremental cost-effectiveness ratios (ICERs) (full economic analysis)
- Results from cost-effectiveness acceptability curves (CEACs)

3.5 Study selection strategy

Two independent reviewers using a pre-piloted screening form screened all identified bibliographic records for title/abstract. Full text reports of all potentially relevant records were then retrieved and examined independently. Disagreements were resolved via discussions and consensus agreement (either between the two reviewers or via a third party).

The study flow and reasons for exclusion of full text papers were documented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram.[42]

3.6 Data extraction strategy

Two reviewers independently extracted relevant data using a pre-defined pre-piloted extraction sheet (Appendix III). The extracted data included details about study (e.g., author, country, design, sample size, follow-up duration, risk of bias items), participant (e.g., age, sex, inclusion/exclusion criteria, CD activity index, clinical/endoscopy definitions of CD remission, type of induction therapy), intervention/comparator (brand name/manufacturer of elemental nutrition; type, mode, duration, and dose of administration of elemental nutrition, any concomitant diet or dietary restriction, and other co-intervention such as medications), and outcome characteristics (e.g., type and scale of measurement, timing of assessment, definition of CD relapse/recurrence). The extracted data were cross-checked by second reviewer and any disagreements were resolved by discussion. Further discrepancies were resolved by a third reviewer, if necessary.

For individual studies, the dichotomous and continuous summary clinical effectiveness outcome measures of association were summarized as risk/odds ratio, mean difference, and measures of variability (p-value, 95% confidence interval). We tried to calculate missing statistical parameters (e.g., risk ratios, mean differences, standard deviations, standard errors, and 95% confidence intervals [CIs]) for clinical outcomes of interest (e.g., maintenance of remission, risk of relapse, time to relapse, incidence of mucosal healing, need for surgery, withdrawals, adherence, adverse events, and complications). All calculated parameters were entered into the data extraction sheets and marked as 'calculated'.

3.7 Risk of bias assessment strategy

Two reviewers independently assessed the methodological and reported quality of included individual studies. Any disagreements between the two reviewers were resolved by a third reviewer through discussion.

RCTs were quality-assessed using the Cochrane Collaboration Risk of Bias (ROB) tool[43] which covers the following domains of threat to internal validity: selection bias (randomisation sequence generation, treatment allocation concealment), performance bias (blinding of participants/personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data primary outcome), reporting bias (selective outcome/analysis reporting), and other pre-specified bias (e.g., funding source, adequacy of statistical methods used, type of analysis, baseline between-group imbalance in important prognostic factors).

The risk of bias assessment falls into three categories of high, low, and unclear risk of bias. The assessments were provided in ROB tables and summary graphs. Non-randomised controlled clinical

trials were assessed using a modified Cochrane ROB tool in which the domain of selection bias was evaluated in regards to baseline between-group imbalance for important prognostic factors instead of randomisation sequence generation and treatment allocation concealment. For each study (RCT or non-RCT), the risk of performance, detection, and attrition bias domains for subjective (e.g., patient-administered clinical or quality of life scores) and objective (e.g., additional laboratory criteria used in the definition of remission/relapse, weight gain, mucosal healing, growth, adverse events) outcomes were assessed separately. Afterwards, within-study summary ROB ratings across all domains were derived for subjective and objective outcome groups separately. At data synthesis stage, across-study average summary ROB ratings were determined and assigned to each outcome of interest (Appendix IV).

The quality of economic analyses of the included studies was planned to be assessed using the Drummond 10-item checklist.[44]

3.8 Data synthesis

Study, treatment, population, and outcome characteristics were summarised in text and summary tables. The study results on the relative effectiveness of elemental nutrition for each outcome of interest were compared qualitatively and quantitatively in text and summary tables.

In the clinical effectiveness part of the review, results for any given outcome measures were presented separately stratified by a comparison category: a) elemental nutrition vs. no intervention (i.e., restricted/unrestricted diet alone), b) elemental nutrition vs. drug (standard therapy), c) elemental nutrition vs. combination of elemental and drug, d) elemental nutrition combination with drug vs. drug alone, and e) elemental nutrition vs. other type of enteral nutrition.

The decision to pool individual study results was based on a degree of similarity with respect to methodological and clinical characteristics of studies under consideration (e.g., design population, comparator treatment, and outcome). Estimates of post-treatment mean difference for continuous outcomes and RRs for binary outcomes (except for rare events) of individual studies were pooled using a DerSimonian and Laird random-effects model.[45] Dichotomous outcomes with low event rates (5.0% - 10.0%) were pooled as RR using a Mantel-Haenszel fixed-effects model. Dichotomous outcomes for studies with very low event rates (≤ 5.0%) or zero events in one of the treatment arms were pooled as odds ratio (OR) using a Peto fixed-effects model.[46] Trials were not pooled if the mean and/or standard deviation for the continuous outcome of interest could not be ascertained.

The degree of statistical heterogeneity across pooled studies was determined through inspection of the forest plots, Cochran's Q and the I^2 statistics. The heterogeneity was judged according to pre-determined levels of statistical significance (Chi^2-based $p<0.10$ and/or $I^2>50\%$). If data allowed, study-level clinical and methodological sources of heterogeneity of effect estimates across studies was explored through a priori defined subgroup analysis (i.e., age, sex, induction therapy) and sensitivity analysis (risk of bias item-specific ratings, intention-to-treat vs. per protocol analysis).
Given a sufficient number of data points, publication bias was planned to be assessed through visual inspection of funnel plots with respect to plot asymmetry and use of linear regression tests.[47]

Results for individual studies were rendered inconclusive in cases of missing/partially reported data (e.g., missing/undetermined summary effect measures and/or corresponding 95% CIs, only p-value reported) or statistically non-significant effect estimates with great uncertainty (i.e., wide intervals that include moderate to large effect size treatment effects in both directions compatible to either benefit or harm of elemental nutrition).

3.9 Overall quality of evidence (GRADE system)

The overall quality of evidence for pre-selected gradable outcome (maintenance of remission, risk of CD relapse/recurrence, mucosal healing, need for surgery, adherence, and adverse events) across studies was assessed using the systematic approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org).

The GRADE approach[48] indicates level of confidence in the observed treatment effect estimate(s) and is based on assessments across five domains: a) summary ROB across studies per gradable outcome (internal validity across studies; study limitations), b) consistency of results (heterogeneity), c) directness of the evidence (applicability of the results), d) precision of the results (the width of 95% CI around the estimate), and e) publication/reporting bias (detection of asymmetry in the funnel plot; selective outcome reporting). The overall quality of evidence was rated as high, moderate, low, or very low grade. Initial grade of RCTs was rated as high and downgraded by one point (e.g. from high to moderate) if any of the five criteria was not met. Initial grade for non-RCTs was to be rated as low and upgraded by one point (e.g. from low to moderate) if any of the three criteria for upgrading a grade was met (e.g., dose-response gradient, large magnitude of effect, and adjustment for confounders).[49]

4 RESULTS

4.1 Literature search

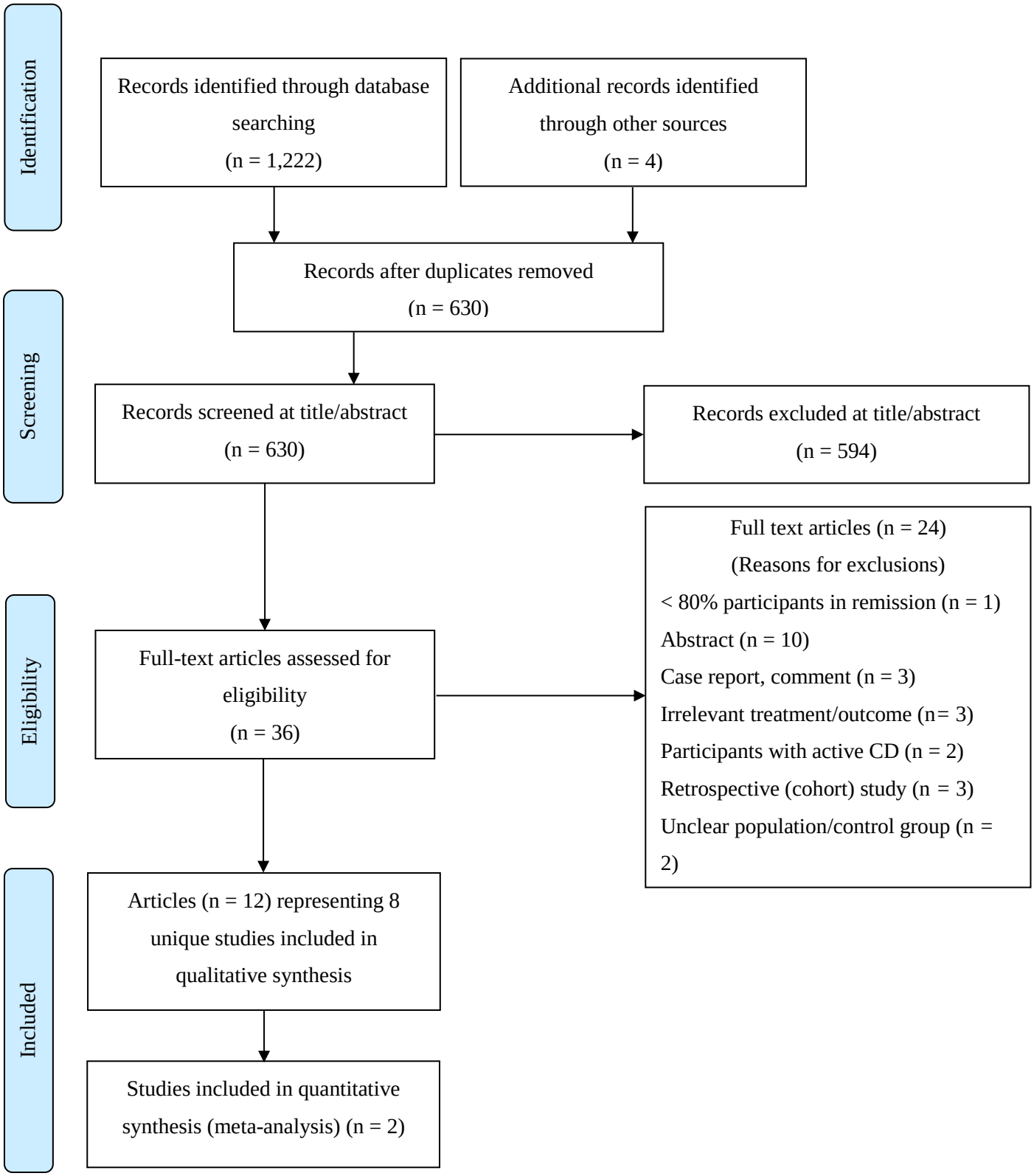
A total of 1,222 records was identified through electronic searches. Four additional records were identified from other sources. The removal of duplicates left 630 records to be screened, of which 594 were excluded at title/abstract level as obviously irrelevant. The remaining 36 records were examined for full-text, of which 12 (representing eight unique studies) were included in the review.[30, 50-60]

Of the eight included studies, one RCT[52, 53] and one non-RCT[30, 59, 60] were represented in multiple publications. Throughout this review, these two studies will be cited according to their corresponding original publications.[30, 52]

The search of on-going trials in Clinical Trials.gov, Current Controlled Trials, UKCRN Portfolio, and WHOICTRP databases (carried out in September 2013) retrieved 26 potentially relevant records, none of which was deemed relevant for inclusion in the review.

The study flow diagram outlining the process of identifying relevant literature and eight included studies[30, 50-52, 55-58] along with reasons for exclusion is given in Figure 1. More details on exclusions can be found in Appendix V.

Figure 1: Study Flow Diagram



4.2 Trial characteristics

This review included three randomised controlled trials (RCTs)[50, 52, 55] and five non-randomised controlled trials (non-RCTs).[30, 51, 56-58]

4.2.1 Randomised controlled trials (RCTs)

The study and participant characteristics of the three included randomised controlled trials (RCTs)[50, 52, 55] are summarised in Table 2. Of three RCTs, two were conducted in Japan[50, 52] and one in the UK.[55] A total of 179 participants was randomised across three RCTs with individual trial sample size ranging from 33[55] to 95[50] participants. The mean age of participants across the three trials ranged from 29[52] to 44 years[55] and the proportion of females from 23%[52] to 68%.[55] The length of follow-up of the studies ranged from 12[52, 55] to 24 months.[50] In most participants CD was located in both the small and large intestines. Induction therapies included parenteral nutrition,[50, 52] central venous feeding,[50] prednisolone,[50, 55] infliximab,[50, 52] 6-MP,[50] enteral nutrition,[52] or surgery.[52] Only two studies[52, 55] reported criteria used for the diagnosis of CD. The diagnosis of CD included clinical, endoscopic, radiological, and/or histological criteria.

In all three trials, the elemental nutrition was given in addition to unrestricted diet (i.e., normal/free diet) through self-inserted feeding tube[50, 52] or oral intake.[50, 52, 55] In one trial,[52] participants in the elemental nutrition group were asked to take half of the daily calories through elemental nutrition (i.e., 'half-elemental diet') and the other half from unrestricted diet. Participants in the control groups were assigned to receive unrestricted diet (no intervention),[50, 52] drug (6-MP),[50] or polymeric nutrition.[55]

Remission was defined using CDAI score of ≤150 either alone or with additional clinical criteria (e.g., absence of diarrhoea and abdominal pain or, ESR<20 mm/h).[55] Similarly relapse was defined as either a CDAI score ≥200 alone or with additional criteria (e.g., the need for an additional medication to suppress worsening symptoms,[50, 52] CDAI score increase by 100 points from baseline).[55]

Table 2: Study and participant characteristics (randomised controlled trials)

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics			
					Elemental nutrition	Control 1	Control 2
Hanai 2012[50] Japan	**Aim:** To evaluate the efficacy of elemental diet and 6-MP vs. no intervention as maintenance therapy in CD **Study setting:** specialty clinic **Length of follow up (# months):** 24 **Funding:** NR	**Inclusion criteria**: age ≥18 years who achieved remission (CDAI < 150) within 30 days of entry to this trial **Exclusion criteria**: Patients with abdominal abscess, stricture (B1 of Vienna and Montreal classification), pregnant women, patients with cardiovascular disorders and history of intolerance to 6-MP	**Elemental nutrition:** Elental (Ajinomoto, Tokyo) at ≥900 kcal/day, taken via self-inserted feeding tube (2 pts) or by oral intake (32 pts). Restricted diet: patients were allowed an intake of 3.5–4.0 kcal/kg/day from food as recommended by a qualified dietician **Control 1:** Drug [6-MP 20-80 mg/day] Unrestricted normal diet **Control 2:** No intervention Unrestricted normal diet	***Patients randomised (n)***	32	30	33
				Age (years) - Mean (SD/range)	30.1 (7.7)	32.5 (8.9)	29.8 (10.3)
				Sex - female n/N (%)	10/32 (31.2)	7/30 (23.3)	8/33 (24.2)
				Weight (kg) - Mean (SD/range)	NR	NR	NR
				BMI (kg/m^2) - Mean (SD/range)	NR	NR	NR
				Smoking n/N (%)	18/32 (56.2)	15/30 (50.0)	18/33 (54.5)
				Duration of CD (mo) - Mean (SD/range)	73.2 (69.6)	67.2 (80.4)	58.8 (75.6)
				CDAI score- Mean (SD/range)	103.4 (21.4)	93.2 (27.8)	89.9 (30.1)
				Location of CD - n/N (%) Ilio-colic type Ileal type Colic type	 19/32 (59.4) 8/32 (25.0) 3/32 (9.4)	 21/30 (70.0) 8/30 (26.7) 2/30 (6.7)	 19/33 (57.6) 11/33 (33.3) 3/33 (9.1)
				Previous bowel resection n/N (%)	NR	NR	NR
				Type of induction therapy (n[%]): parenteral nutrition (70/95 [73.7]), central venous feeding (25/95 [26.3]), prednisolone (9/95 [9.5]), infliximab (4/95 [4.2]), 6-MP (14/95 [14.7]) **Total N received induction therapy**: NR **Total N achieving remission after induction therapy**: 105 **Total N allocated to maintenance treatment**: 95 **Diagnostic criteria used for CD:** NR **Co-interventions**: 5-ASA (2250–3000 mg/day), Sulphasalazine (3000 mg/day) **Outcome definitions applied:** Remission (CDAI < 150), Relapse/recurrence (CDAI ≥200 or the need for an additional medication to suppress worsening symptoms) **Outcomes reported:** Maintenance of remission, risk of relapse, adverse events, complications, need of surgery			
Takagi 2006[52-54] Japan	**Aim:** To compare relapse rates in patients with inactive CD receiving half elemental	**Inclusion criteria**: CD patients if they had just undergone induction of remission	**Elemental nutrition:** Elental (AJINOMOTO PHARMA Co., Tokyo, Japan) through	***Patients randomised (n)***	26	25	
				Age (years) - Mean (SD/range)	30.8 (11.1)	28.9 (8.1)	
				Sex - female n/N (%)	6/26 (23.1)	8/25 (32.0)	
				Weight (kg) - Mean (SD/range)	NR	NR	

	nutrition (elemental nutrition + unrestricted diet) vs. no intervention (unrestricted diet) **Study setting:** specialty clinic **Length of follow up (# months):** 12 **Funding:** no external funding received	**Exclusion criteria**: NR	a self-inserted tube and/or oral intake Patients took half the amount of their daily allowance of calories by elemental nutrition and the remaining half by usual unrestricted meals **Control:** No intervention; patients took all nutrients via their usual un-restricted meals	***BMI (kg/m^2) - Mean (SD/range)***	20.1 (3.1)	20.0 (3.6)
				Smoking n/N (%)	NR	NR
				Duration of CD (mo) - Mean (SD/range)	49.2 (50.4)	67.2 (78.0)
				CDAI score- Mean (SD/range)	101.8 (34.1)	86.4 (31.3)
				Location of CD - n/N (%) Small bowel only Colon only Both	 8/26 (30.7) 3/26 (11.5) 15/26 (57.7)	 7/25 (28.0) 6/25 (24.0) 12/25 (48.0)
				Previous bowel resection n/N (%)	11/26 (42.3)	11/25 (44.0)
				Type of induction therapy (n[%]): elemental enteral nutrition 22/51 [43.1] (1800–2100 kcal/day) for 6–8 weeks; total parenteral nutrition 25/51 [49.0] (1500–2100 kcal/day) for 6–8 weeks; oral/IV prednisolone 1/51 [2.0] (40 mg/day, then tapered down every 2 weeks by 5–10 mg); 5 mg/kg IV infliximab 3/51 [5.9], and/or surgery (5/51 [7.9]) **Total N received induction therapy**: 82 **Total N achieving remission after induction therapy**: 56 **Total N allocated to maintenance treatment**: 51 **Diagnostic criteria used for CD:** clinically, endoscopically, radiologically and/or histologically (diagnostic criteria as defined by the Ministry of Health, Labour and Welfare of Japan) **Co-interventions**: Mesalazine (2250–3000 mg/day), Azathioprine (50 mg/day) **Outcome definitions applied:** remission **(**CDAI<150), relapse/recurrence (CDAI > 200, or the need for therapy to induce remission) **Outcomes reported:** risk of relapse, HQOL, adherence		
Verma 2001[55] UK	**Aim:** To compare safety and efficacy of elemental and polymeric nutrition for the maintenance of remission, risk of relapse, and intolerance **Study setting:** specialty clinic	**Inclusion criteria**: inactive CD and steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence	**Elemental nutrition:** Orally taken (EO28, Scientific Hospital Supplies Ltd, Liverpool, UK); sachets containing powdered feed mixed with tap water (20 g/100 ml); the mean daily	***Patients randomised (n)***	19	14
				Age (years) - Mean (SD/range)	41.7 (5.4)	44.1 (3.2)
				Sex - female n/N (%)	13/19 (68.4)	9/14 (64.3)
				Weight (kg) - Mean (SD/range)	62.4 (3.4)	71.4 (7.7)
				BMI (kg/m^2) - Mean (SD/range)	21.8 (1.2)	24.4 (1.6)
				Smoking n/N (%)	NR	NR
				Duration of CD (mo) - Mean (SD/range)	154.4 (37.2)	123.6 (26.4)
				CDAI score- Mean (SD/range)	106.4 (14.9)	90.4 (17.8)

	Length of follow up (# months): 12 **Funding:** NR	during or after 30 d of withdrawal **Exclusion criteria**: recurrent small-bowel obstruction due to Crohn's strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent	intake 730 (range 600–1017) Kcal Unrestricted normal diet **Control:** Orally taken Polymeric nutrition (Fortisip, Nutricia, UK); ready-to-drink cartons (200 ml); the mean daily intake 730 (range 600–1017) Kcal Unrestricted normal diet	***Location of CD - n/N (%)*** Small bowel Large bowel Mixed anastamotic	 7/19 (36.8) 4/19 (21.0) 2/19 (10.5)	 6/14 (42.8) 4/14 (28.6) 0/14 (0.0)
				Previous bowel resection n/N (%)	NR	NR
				Type of induction therapy (n[%]): prednisolone (33 [100%]) **Total N received induction therapy**: NR **Total N achieving remission after induction therapy**: NR **Total N allocated to maintenance treatment**: 33 **Diagnostic criteria used for CD**: standard clinical, radiological, endoscopic and histological criteria **Co-interventions**: Steroids/prednisolone (6.5-7.1 mg), Azathioprine (dose: NR), 5-ASA (dose: NR) **Outcome definitions applied**: remission (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h); relapse/recurrence (CDAI ≥200 or increased by 100 points from baseline) **Outcomes reported**: Maintenance of remission, risk of relapse, adherence, withdrawal from steroids		
ASA=aminosalicylic acid; BMI=body mass index; CD=Crohn's Disease; mo=month(s); CDAI=Crohn's Disease Activity Index; HQOL=health related quality of life; MP=mercaptopurine; N=number; NR=not reported; pts=patients; SD=standard deviation						

4.2.2 Non-randomised controlled trials (non-RCTs)

The study and participant characteristics of the five included non-randomised controlled trials (non-RCTs)[30, 51, 56-58] are summarised in Table 3. Of five studies, four were conducted in Japan[30, 51, 57, 58] and one in the UK.[56] A total of 236 participants were assigned to the study treatments. The number of participants across the studies ranged from 39[56] to 61.[51] The mean age in the studies ranged from 22[51] to 42 years[56] and the proportion of females from 13%[51] to 72%.[56] The length of follow up ranged from 12[30, 57] to 48 months.[51] One trial included exclusively those participants who had earlier undergone bowel resection surgery for CD.[30] The majority of participants had both small and large bowel involvement of CD. Only one study reported the diagnostic criteria of CD.[51] Induction therapies were prednisolone,[56, 57] azathioprine,[56] 5-ASA,[30, 56, 57] infliximab,[57, 58] corticosteroid,[30] bowel resection,[30] parenteral nutrition,[57] and elemental nutrition.[51, 57]

In all five trials, the elemental nutrition was given in addition to either restricted[30, 51, 57, 58] or unrestricted diet (i.e., normal/free diet)[56] through feeding tube infusion[30, 51, 57, 58] or oral intake.[56] Participants in the elemental nutrition groups were asked to take half of the daily calories through elemental nutrition.[30, 57, 58] The elemental nutrition groups received either elemental nutrition alone[30, 51, 56, 57] or elemental nutrition with drug (sulfasalazine/prednisolone[51] or infliximab[58]). Participants in the control groups were assigned to receive unrestricted/restricted diet (no intervention),[30, 51, 56, 57] drug only (sulfasalazine/prednisolone[51] or infliximab[58]).

Remission was defined clinically using CDAI score<150 alone[30, 56-58] or with additional clinical/endoscopic criteria such as normal values of IOIBD, erythrocyte sedimentation rate (ESR) and CRP scores[51] or Rutgeerts score<2.[30, 57] Relapse/recurrence was defined by subjective/objective symptoms (increase of the IOIBD score by ≥2, enhanced ESR/CRP;[51] increase in CDAI by >100 points after baseline, or final CDAI score >150, need of surgery, or increased doses of steroids;[56] or CDAI scores ≥ 150).[30, 57, 58]

Table 3: Study and participant characteristics (non-randomised controlled trials)

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics				
					Elemental nutrition	Control 1	Control 2	Control 3
Hirakawa 1993[51] Japan	**Aim:** To compare the effects of elemental nutrition alone, combination of elemental nutrition and drugs, drugs alone, and no intervention on maintenance of remission in CD patients **Study setting:** primary care **Length of follow up (# months):** 48 **Funding:** NR	**Inclusion criteria:** patients with CD in remission **Exclusion criteria:** patients with active CD	**Elemental nutrition:** Elemental nutrition (Brand: NR) via nasoenteral tube (with restricted diet) **Control 1:** Elemental nutrition + Drug [sulfasalazine 3g/d or prednisolone 10mg/d] (with restricted diet) **Control 2:** Drug [sulfasalazine 3g/d or prednisolone 10mg/d] (with restricted diet) **Control 3:** No intervention (with restricted diet)	***Patients assigned (n)***	25	22	8	6
				Patients analysed (n)	22	17	8	6
				Age (years) - Mean (SD/range)	27.0 (7.4)	26.6 (2.4)	21.9 (2.6)	25.7 (5.0)
				Sex - female n/N (%)	3/22 (13.6)	6/17 (35.3)	3/8 (37.5)	2/6 (33.3)
				Weight (kg) - Mean (SD/range)	NR	NR	NR	NR
				BMI (kg/m^2) - Mean (SD/range)	NR	NR	NR	NR
				Smoking n/N (%)	NR	NR	NR	NR
				Duration of CD (mo) - Mean (SD/range)	NR	NR	NR	NR
				CDAI score- Mean (SD/range)	61.6 (29.2)	56.0 (26.6)	68.5 (30.2)	69.3 (52.1)
				Location of CD - n/N (%) Small bowel Large bowel Small and large bowel	 5/22 (22.7) 1/22 (4.5) 16/22 (72.7)	 0/17 (0.0) 3/17 (17.6) 14/17 (82.3)	 0/8 (0.0) 2/8 (25.0) 6/8 (75.0)	 0/6 (0.0) 0/6 (0.0) 6/6 (100.0)
				Previous bowel resection n/N (%)	NR	NR	NR	NR
				Type of induction therapy (n[%]): elemental nutrition (25/53 [47.1]), elemental nutrition and drugs (23/53 [43.4]), drugs alone (5/53 [9.4]) **Total N received induction therapy:** 84 **Total N achieving remission after induction therapy:** 67 **Total N allocated to maintenance treatment:** 61 **Diagnostic criteria used for CD:** Criteria of the Japanese Society Gastroenterology **Co-interventions:** NR **Outcome definitions applied:** remission IOIBD score (value: NR) and normal values of ESR and CRP, relapse/recurrence of subjective/objective symptoms (increase of the IOIBD score by ≥2, enhanced ESR, and positive CRP) **Outcomes reported:** cumulative continuous remission rate				

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics			
					Elemental nutrition	Control 1	Control 2
Verma 2000[56] UK	**Aim:** To evaluate clinical effectiveness of adding elemental nutrition taken orally to normal food for maintaining remission in patients with quiescent CD over 12 months **Study setting:** specialty clinic **Length of follow up (# months):** 24 **Funding:** NR	**Inclusion criteria:** Patients with quiescent disease defined by the absence of bowel symptoms and CDAI<150 who had been treated with either elemental nutrition or prednisolone as an induction therapy within preceding 12 months **Exclusion criteria:** CDAI>150, sepsis, bowel strictures leading to recurrent attacks of small bowel obstruction or previous intolerance to enteral feeding	**Elemental nutrition:** Elemental nutrition "EO28 Extra" powder taken orally in three separate portions daily (with normal unrestricted diet) **Control 1:** No intervention (i.e., normal unrestricted diet) **Control 2:** NA	***Patients assigned (n)***	21	18	NA
				Patients analysed (n)	17	18	NA
				Age (years) - Mean (SD/range)	39.2 (3.9)	42.0 (3.3)	NA
				Sex - female n/N (%)	14/21 (66.6)	13/18 (72.2)	NA
				Weight (kg) - Mean (SD/range)	59.4 (2.9)	62.7 (2.8)	NA
				BMI (kg/m^2) - Mean (SD/range)	20.0 (2.2)	22.9 (0.9)	NA
				Smoking n/N (%)	NR	NR	NA
				Duration of CD (mo) - Mean (SD/range)	60.3 (18.4)	91.0 (14.8)	NA
				CDAI score- Mean (SD/range)	112.8 (11.5)	94.6 (7.1)	NA
				Location of CD - n/N (%) Small bowel Large bowel Mixed bowel Anastomotic	10/17 (58.8) 5/17 (29.4) 6/17 (35.3) 0/17 (0.0)	7/18 (38.8) 5/18 (27.7) 3/18 (16.6) 3/18 (16.6)	NA
				Previous bowel resection n/N (%)	NR	NR	NA

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics			
					Elemental nutrition	**Control 1**	**Control 2**
				Type of induction therapy (n[%]): medical (prednisolone, azathioprine, 5-ASA) **Total N received induction therapy:** 46 **Total N achieving remission after induction therapy:** 39 **Total N allocated to maintenance treatment:** 39 **Diagnostic criteria used for CD:** standard clinical, endoscopic, radiological, and when possible, histological criteria **Co-interventions:** Prednisolone (mean range: 10.5-17.5 mg/d) azathioprine (dose: NR) 5-ASA (dose: NR) **Outcome definitions applied:** remission CDAI<150, relapse/recurrence increase in CDAI by >100 points since baseline or final CDAI >150 points; need of surgery; increased doses of steroids **Outcomes reported:** maintenance of clinical remission at 12 mo, withdrawal from steroids, and duration of remission at 24 mo			
Yamamoto 2010[58] Japan	**Aim:** to assess the efficacy of EN on the maintenance rate of clinical remission in patients with quiescent CD receiving infliximab as maintenance therapy **Study setting:** specialty clinic **Length of follow up (# months):** 14 **Funding:** NR	**Inclusion criteria:** patients diagnosed with CD who had achieved clinical remission (CDAI<150 after infliximab induction therapy) with time from the induction of remission to entry ≤2 weeks; patients who had experienced EN therapy including elemental nutrition infusion at least one time before entry; and patients who agreed to continue with the assigned treatment (with or without concomitant enteral nutrition) for 56 weeks **Exclusion criteria:** patients who had severe anorectal involvement; patients	**Elemental nutrition:** Elemental nutrition via nasogastric tube infusion during night-time (Elental (Ajinomoto, Tokyo)) + Drug [infliximab 5 mg/kg] (with restricted low fat diet) **Control 1:** Drug [Infliximab 5 mg/kg] (with unrestricted low fat diet) **Control 2:** NA	***Patients assigned (n)***	32	24	NA
				Patients analysed (n)	32	24	NA
				Age (years) - Mean (SD/range)	31.0 (9.0)	33.0 (7.8)	NA
				Sex - female n/N (%)	12/32 (37.5)	8/24 (33.3)	NA
				Weight (kg) - Mean (SD/range)	NR	NR	NA
				BMI (kg/m^2) - Mean (SD/range)	NR	NR	NA
				Smoking n/N (%)	4/32 (12.5)	4/24 (16.6)	NA
				Duration of CD (mo) - Mean (SD/range)	33.0 (24.8)	35.0 (19.6)	NA
				CDAI score- Mean (SD/range)	102.1 (18.1)	102.3 (22.5)	NA

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics			
					Elemental nutrition	**Control 1**	**Control 2**
		who had tight bowel strictures or enteric fistulae even if clinical symptoms were quiescent		***Location of CD - n/N (%)*** Small bowel Small bowel and colon	11/32 (34.4) 21/32 (65.6)	11/24 (45.8) 13/24 (54.1)	NA
				Previous bowel resection n/N (%)	11/32 (34.4)	8/24 (33.3)	NA
				Type of induction therapy (n[%]): medical (infliximab 5 mg/kg) **Total N received induction therapy:** NR **Total N achieving remission after induction therapy:** 56 **Total N allocated to maintenance treatment:** 56 **Diagnostic criteria used for CD:** NR **Co-interventions:** Mesalazine (Pentasa 3 g/day), Azathioprine (Imuran 50–100 mg/day) **Outcome definitions applied:** remission CDAI < 150, relapse/recurrence score CDAI > 150 **Outcomes reported:** remission maintenance rate, time to relapse			
Yamamoto [30, 59, 60] Japan	**Aim:** to examine if long-term elemental nutrition infusion along with low fat diet is useful in reducing clinical and endoscopic recurrence rates after resection for CD **Study setting:** specialty clinic **Length of**	**Inclusion criteria:** patients with endoscopic and histological diagnosis of CD, aged 15-75 yrs who had resection for ileal and ileocolonic (including ileocaecal) CD; received EN therapy including elemental nutrition infusion at least once before operation; agreed to continue assigned treatment (with or without enteral nutrition) for more than 1 year after operation **Exclusion criteria:** patients with colonic CD alone or with diffuse small bowel CD	**Elemental nutrition:** Elental (Ajinomoto, Tokyo, Japan) infused at home nasogastrically via self-intubated tube in the night-time 1 week after operation (with restricted food diet) **Control 1:** No intervention (i.e., normal unrestricted	***Patients assigned (n)***	20	20	NA
				Patients analysed (n)	20	20	NA
				Age (years) - Mean (SD/range)	31.0 (16.5)	33.0 (17.4)	NA
				Sex - female n/N (%)	8/20 (40.0)	6/20 (30.0)	NA
				Weight (kg) - Mean (SD/range)	NR	NR	NA
				BMI (kg/m^2) - Mean (SD/range)	NR	NR	NA
				Smoking n/N (%)	2/20 (10.0)	2/20 (10.0)	NA
				Duration of CD (mo) - Mean (SD/range)	37.0 (31.7)	39.0 (36.7)	NA

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics			
					Elemental nutrition	**Control 1**	**Control 2**
	follow up (# months): 12 **Funding:** no external funding received		diet) **Control 2:** NA	***CDAI score- Mean (SD/range)***	NR	NR	NA
				Location of CD - n/N (%) Terminal ileum Terminal ileum and colon Ileocolonic anastomosis	5/20 (25.0) 11/20 (55.0) 4/20 (20.0)	7/20 (35.0) 9/20 (45.0) 4/20 (20.0)	NA
				Previous bowel resection n/N (%)	20/20 (100.0)	20/20 (100.0)	NA
				Type of induction therapy (n[%]): bowel resection (40/40 [100.0]), corticosteroids (37/40 [92.5]), pentasa (32/40 [77.5]) **Total N received induction therapy:** NR **Total N achieving remission after induction therapy:** NR **Total N allocated to maintenance treatment:** 40 **Diagnostic criteria used for CD:** endoscopic and histological (no specific criteria reported) **Co-interventions:** Pentasa 3000 mg/day as a prophylactic medication. No corticosteroid, immunosuppressive drugs, or infliximab except patients who relapsed **Outcome definitions applied:** remission CDAI<150 (clinical), Rutgeerts score<2 (endoscopic), relapse/recurrence clinical (at 6, 12 mo: CDAI≥150; at 60 mo: CDAI≥200), endoscopic (Rutgeerts score≥2) **Outcomes reported:** clinical and endoscopic recurrence			
Yamamoto 2007b[57] Japan	**Aim:** To investigate if long-term enteral nutrition (vs. no intervention) is effective in reducing	**Inclusion criteria:** patient with endoscopic/histological diagnosis of CD in the terminal ileum and/or the colon; age: 15-75 years; clinical remission (CDAI<150) after medical	**Elemental nutrition:** Elemental nutrition: Elental (Ajinomoto, Tokyo)(with restricted food	***Patients assigned (n)***	20	20	NA
				Patients analysed (n)	20	20	NA
				Age (years) - Mean (SD/range)	29.0 (17.4)	31.0 (20.1)	NA
				Sex - female n/N (%)	6/20 (30.0)	7/20 (35.0)	NA

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics			
					Elemental nutrition	Control 1	Control 2
	clinical and endoscopic relapse rates and inhibiting mucosal cytokine production in patients with quiescent CD **Study setting:** NR **Length of follow up (# months):** 12 **Funding:** NR	treatment; the duration from the induction of remission to entry<8 weeks; patients had experienced enteral nutrition therapy including elemental nutrition infusion at least 1 time before entry; patient agreed to continue with assigned treatment (with or without enteral nutrition) for >1 year; and patient agreed to have ileocolonoscopy with multiple mucosal biopsies even if they did not have any clinical symptoms **Exclusion criteria:** diffuse jejunoileal or gastroduodenal; severe anorectal stricture or sepsis; tight bowel strictures or enteric fistulae even though clinical symptoms were quiescent; patient had	diet) **Control 1:** no intervention (i.e., normal unrestricted diet **Control 2:** NA	***Weight (kg) - Mean (SD/range)***	51.1 (8.5)	48.9 (7.6)	NA
				BMI (kg/m^2) - Mean (SD/range)	19.2 (1.3)	19.1 (1.8)	NA
				Smoking n/N (%)	2/20 (10.0)	4/20 (20.0)	NA
				Duration of CD (mo) - Mean (SD/range)	32.0 (35.3)	36.0 (38.9)	NA
				CDAI score- Mean (SD/range)	101.0 (28.2)	92.0 (21.5)	NA
				Location of CD - n/N (%) Terminal ileum Colon Terminal ileum and colon	7/20 (35.0) 2/20 (10.0) 11/20 (55.0)	8/20 (40.0) 2/20 (10.0) 10/20 (50.0)	NA
				Previous bowel resection n/N (%)	4/20 (20.0)	4/20 (20.0)	NA

Author year Ref ID Country	Study details	Inclusion/ exclusion criteria	Interventions	Patient characteristics			
					Elemental nutrition	Control 1	Control 2
		received corticosteroids, immunosuppressive drugs, or infliximab at entry		**Type of induction therapy (n[%]):** 4 pts (5 mg/kg x 1 or x 3 prednisolone, infliximab), 6 pts (prednisolone with enteral nutrition), 10 pts (prednisolone alone), 20 pts (enteral nutrition alone), 36 pts (Pentasa 750–3000 mg/day), and the majority of patients required parenteral nutrition at the start of the treatment **Total N received induction therapy:** NR **Total N achieving remission after induction therapy:** NR **Total N allocated to maintenance treatment:** 40 **Diagnostic criteria used for CD:** endoscopic and histological (not specified) **Co-interventions:** Pentasa 3000 mg/day as a prophylactic medication. No corticosteroid, immunosuppressive drugs, or infliximab except patients who relapsed **Outcome definitions applied:** remission CDAI<150 (clinical), NR (endoscopic; specific threshold for the mucosal inflammation grade NR), relapse/recurrence CDAI≥150 (clinical), NR (endoscopic; specific threshold for the mucosal inflammation grade NR) **Outcomes reported:** CDAI score, cumulative proportion of patients maintaining clinical remission (CDAI<150), endoscopic severity of disease activity/mucosal inflammation, mucosal cytokine assays			

ASA=aminosalicylic acid; BMI=body mass index; CD=Crohn's Disease; mo=month(s); CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; EN=Enteral nutrition; ESR=erythrocyte sedimentation rate; HQOL=health related quality of life; IOBD=International Organization for the Study of Inflammatory Bowel Disease; N=number; NR=not reported; pts=patients; SD=standard deviation

4.3 Risk of bias assessment

Risk of bias assessment for the eight included studies (three RCTs[50, 52, 55] and five non-RCTs[30, 51, 56-58]) are presented in risk of bias tables and graphs separately for RCTs (Table 4; Figure 2) and non-RCTs (Table 5; Figure 3).

4.3.1 Randomised controlled trials (RCTs)

Overall, two[50, 52] of the three RCTs reported an adequate method for random sequence generation and only one[52] reported adequate treatment allocation concealment (low risk of bias). All three RCTs were rated as having low risk of performance and detection bias for objective (e.g., radiography, endoscopy) vs. subjective (e.g., patient-administered functional scores, CDAI) outcomes. The RCTs failed to report blinding status of the patients and study personnel. But based on the nature of the administered intervention, it is unlikely that study personnel and participants in these studies were blinded. In two RCTs,[50, 55] it was not clear if outcome assessors were blinded. Outcome assessors in one RCT[52] were reported to be blinded. For the three RCTs, the influence of attrition bias was judged at low risk. All three RCTs were judged as being at high risk for selective outcome and/or analysis bias. Risk of other bias (e.g., funding source, balance imbalance in important characteristics, inappropriate analysis) for two RCTs[50, 52] was judged to be low.

4.3.2 Non-randomised controlled trials (non-RCTs)

The presence of imbalance in important baseline factors was suspected for two non-RCTs (high risk of bias)[51, 56] and was unclear for the remaining three non-RCTs.[30, 57, 58] In the first trial,[51] there was some between-group imbalance in induction therapy and distribution of the lesion. In the second trial,[56] the elemental nutrition group had a shorter disease duration (60.3 vs. 91.0 months), greater ESR, and a longer steroid use compared to the no intervention group. Four non-RCTs[30, 56-58] were rated as having low risk of performance and detection bias for objective (e.g., radiography, endoscopy) vs. subjective (e.g., patient-administered functional scores, CDAI) outcomes. Three RCTs[51, 56, 58] failed to report blinding status of the patients, study personnel, as well as outcome assessors. Based on the nature of the administered intervention in these studies, it is unlikely that study personnel and participants were blinded. The remaining two non-RCTs[30, 57] explicitly reported that patients and study personnel were not blinded, but outcome assessors were blinded. For four non-RCTs,[30, 56-58] the influence of attrition bias was judged at low risk. Three of the five non-RCTs[30, 57, 58] were judged as being at low risk for selective outcome and/or analysis bias. Risk of other bias (e.g., funding source, balance imbalance in important characteristics, inappropriate analysis) for four non-RCTs[30, 56-58] was judged to be low.

Table 4: Risk of bias for randomised controlled trials: review author's judgments about each risk of bias item

First author, year, study ID	**Selection bias** Random sequence generation	**Selection bias** Allocation concealment	**Performance bias** Subjective (e.g., patient-reported)	**Performance bias** Objective (e.g., radiography, endoscopy)	**Detection bias** Subjective (e.g., patient-reported)	**Detection bias** Objective (e.g., radiography, endoscopy)	**Attrition bias** Subjective (e.g., patient-reported)	**Attrition bias** Objective (e.g., radiography, endoscopy)	**Reporting bias** Selective reporting of the outcome, subgroups, or analysis	**Other bias** Funding source, adequacy of statistical methods used, type of analysis [ITT/PP], baseline imbalance in important characteristics
Hanai 2012[50]	+	?	-	+	-	+	+	+	-	+
Takagi 2006[52-54]	+	+	-	+	-	+	+	+	-	+
Verma 2001[55]	?	?	-	+	-	+	+	+	-	?

ID=identification; ITT=intention-to-treat; PP=per protocol

Key:

- High risk of bias
? Unclear risk of bias
+ Low risk of bias
NA Not applicable

Table 5: Risk of bias for non-randomised controlled trials: review author's judgments about each risk of bias item

First author, year, study ID	**Selection bias** The presence/absence of baseline between-group imbalance in important prognostic factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)	**Performance bias** Subjective (e.g., patient-reported)	**Performance bias** Objective (e.g., radiography, endoscopy)	**Detection bias** Subjective (e.g., patient-reported)	**Detection bias** Objective (e.g., radiography, endoscopy)	**Attrition bias** Subjective (e.g., patient-reported)	**Attrition bias** Objective (e.g., radiography, endoscopy)	**Reporting bias** Selective reporting of the outcome, subgroups, or analysis	**Other bias** Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]
Hirakawa 1993[51]	−	NA	+	NA	+	NA	−	−	−
Verma 2000[56]	−	−	+	−	+	+	+	−	+
Yamamoto 2007a[30, 60]	?	−	+	−	+	+	+	+	+
Yamamoto 2007b[57]	?	−	+	−	+	+	+	+	+
Yamamoto 2010[58]	?	−	+	−	+	+	+	+	+

ID=identification; ITT=intention-to-treat; PP=per protocol

Key:

− High risk of bias ? Unclear risk of bias + Low risk of bias NA Not applicable

Figure 2: Overall risk of bias assessment: randomised controlled trials

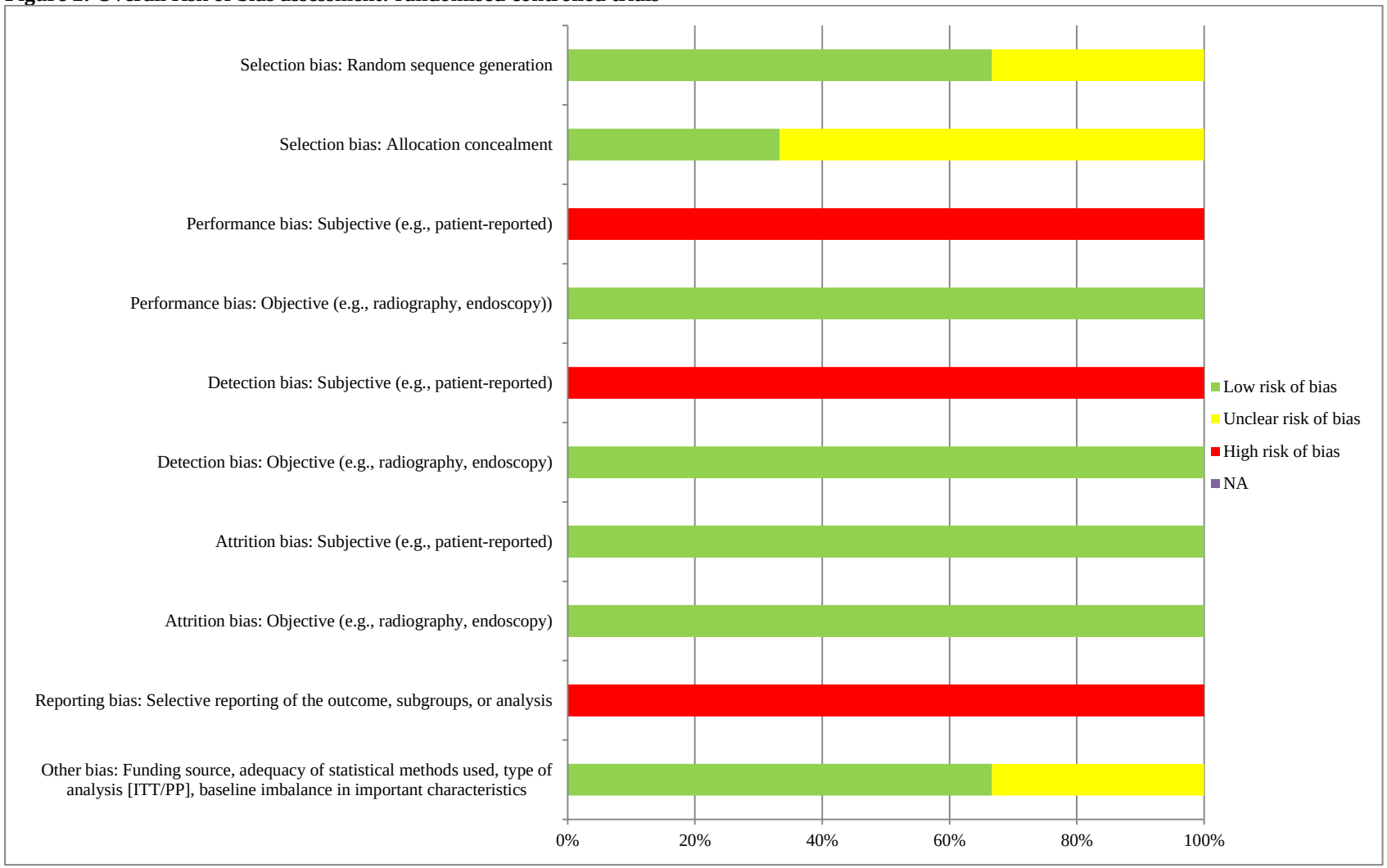
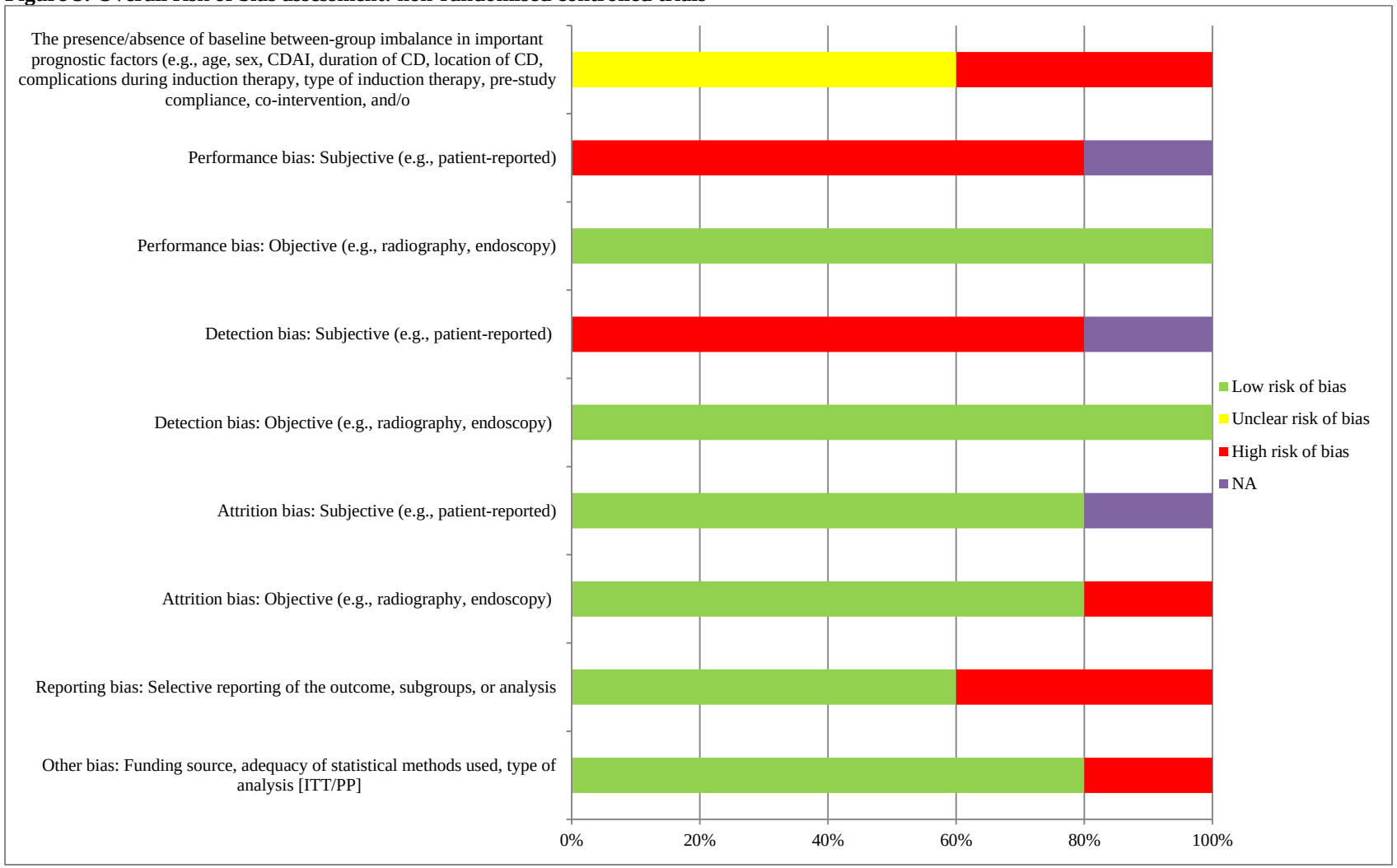


Figure 3: Overall risk of bias assessment: non-randomised controlled trials



4.4 Clinical effectiveness of elemental nutrition

Results of included trials are provided in Table 6 to Table 24. Results reported partially (e.g., missing effect measures, 95% CIs) or statistically non-significant effect measures with wide 95% CIs were considered inconclusive.

4.4.1 Maintenance of Remission

In seven of the eight included trials, the maintenance of remission was reported as the proportion of patients maintaining remission[30, 50, 55-58] and/or cumulative probability of maintaining remission (Kaplan Meier estimates of survival).[50, 51, 57, 58] This outcome was not reported for one trial.[52] None of the trials reported duration of remission. See Table 6 to Table 9.

Elemental nutrition vs. No intervention (i.e., unrestricted/free or restricted diet)

Randomised controlled trials

In one trial,[50] the post-treatment differences for the maintenance of remission at 6 and 12 months were not statistically significant between the elemental nutrition and no intervention groups [review conclusion: inconclusive]. However, at 24 months of follow-up, elemental nutrition was significantly more beneficial in maintaining remission compared to no intervention (RR=2.06, 95% CI: 1.00, 4.43). The same trial reported statistically significantly greater cumulative probability for being in remission for the participants who received elemental nutrition vs. no intervention at 18 (p=0.04) and 24 months of follow-up (p=0.03) [review conclusion: inconclusive]. See Table 6 and Table 7.

Non-randomised controlled trials

Two of the three trials,[30, 56, 57] reporting maintenance of remission (i.e., proportion of patients maintaining remission), indicated significantly greater rates of maintenance in favour of elemental nutrition at 12 months post-baseline.[30, 57] For example, in one of these trials,[57] significantly more participants receiving elemental nutrition maintained their remission at 12 months of follow-up (RR=2.14, 95% CI: 1.12, 4.10). The results regarding maintenance of remission reported in one trial[56] and cumulative probability of maintaining remission at 48 months reported in one trial (no intervention: restricted diet)[51] were rendered inconclusive due to wide statistically non-significant 95% CIs[56] and partially reported data (missing effect estimates and 95% CIs), respectively.[51] See Table 8 and Table 9.

Elemental nutrition vs. Drug

Randomised controlled trials

In one trial,[50] the maintenance rate of remission (i.e., proportion of patients maintaining remission and cumulative probability of maintaining remission) at 6 to 24 months of follow-up was not significantly different between the participants receiving elemental nutrition and 6-mercaptopurine (6-MP). Due to missing effect estimates (for the cumulative probability of maintaining remission) and wide 95% CIs (for the proportion of patients maintaining remission), this result was deemed inconclusive. See Table 6 and Table 7.

Non-randomised controlled trials

One trial[51] showed significantly greater cumulative probability of maintaining remission in participants receiving elemental nutrition vs. those on sulfasalazine/prednisolone at 48 months of follow-up (63% vs. 0%, $p<0.05$). However, due to partially reported data (i.e., missing 95% CIs), this result was deemed inconclusive. See Table 8 and Table 9.

Elemental nutrition vs. Elemental nutrition plus drug

Randomised controlled trials

No trial with these comparisons

Non-randomised controlled trials

In one trial,[51] the cumulative probability of maintaining remission was not significantly different for the participants receiving elemental nutrition vs. elemental nutrition plus sulfasalazine or prednisolone at 48 months of follow-up (63% vs. 66%, $p>0.05$). Due to partially reported data (i.e., missing 95% CIs), this result was deemed inconclusive. See Table 8 and Table 9.

Elemental nutrition plus drug vs. Drug

Randomised controlled trials

No trial with these comparisons.

Non-randomised controlled trials

In one trial,[58] the proportion of patients maintaining remission (RR=1.17, 95% CI: 0.83, 1.64) and cumulative probability of maintaining remission ($p=0.32$) were not significantly different in the elemental nutrition plus infliximab vs. infliximab alone group at 14 months of follow-up [review conclusion: inconclusive]. In contrast, another trial[51] showed a significant effect of adding elemental nutrition to sulfasalazine/prednisolone compared to sulfasalazine/prednisolone alone on the cumulative probability of maintaining remission at 48 months post-baseline (66% vs. 0%, $p<0.05$) [review conclusion: inconclusive]. See Table 8 and Table 9.

Elemental nutrition vs. Polymeric nutrition

Randomised controlled trials

In one trial,[55] the proportion of participants maintaining remission was not significantly different between the groups receiving elemental and polymeric nutrition at 12 months of follow-up (RR=0.98, 95% CI: 0.44, 2.19) [review conclusion: inconclusive]. See Table 6.

Non-randomised controlled trials

No trial with these comparisons.

Table 6: Proportion of patients maintaining remission¥ (n/N) – Randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[52]	NR	1 [NA]	No evidence
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
	Elemental nutrition vs. 6-MP	**Elemental nutrition vs. 6-MP**	1 [high ROB]	Inconclusive (elemental nutrition vs. 6-MP)
6 mo	27/32 (84.4) vs. 24/30 (80.0)[50]			
12 mo	20/32 (62.5) vs. 20/30 (66.7)[50]	RR=1.05 (0.83, 1.33)[£]		
24 mo	14/32 (46.9) vs. 17/30 (56.7)[50]	RR=0.93 (0.64, 1.35)[£]		
		RR=0.77 (0.46, 1.27)[£]		
	Elemental nutrition vs. NI			Inconclusive (elemental nutrition vs. NI at 6-12 mo)
6 mo	27/32 (84.4) vs. 23/33 (69.6)[50]	**Elemental nutrition vs. NI**		
12 mo	20/32 (62.5) vs. 15/33 (45.5)[50]	RR=1.21 (0.92, 1.58)[£]		
24 mo	14/32 (46.9) vs. 7/33 (21.2)[50]	RR=1.37 (0.86, 2.17)[£]		
		RR=2.06 (1.00, 4.43)[£]		In favour of elemental nutrition (vs. NI) at 24 mo
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	8/19 (42.1) vs. 6/14 (42.8)[55] (remission: CDAI plus other criteria)	p=NR [NS] RR=0.98 (0.44, 2.19)[£]	1 [unclear ROB]	Inconclusive

95% CI=95 percent confidence interval; CDAI=crohn's disease activity index; MP=mercaptopurine; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; mo=month(s); RCT=randomised controlled trial; RR=risk ratio (relative risk); SD=standard deviation; SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated
[¥] Remission defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria in addition)

Table 7: Cumulative survival rate for being in remission (%) – Randomised controlled trials

Follow-up	Arm-specific Kaplan-Meier survival rate estimates	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[52]	NR	1 [NA]	No evidence
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
	Elemental nutrition vs. 6-MP	**Elemental nutrition vs. 6-MP**		
6 mo	NR[50]		1 [high ROB]	Inconclusive
12 mo	NR[50]	p=0.83 [NS]		
18 mo	NR[50]	p=0.54 [NS]		
24 mo	NR[50]	p=0.41 [NS]		
		p=0.31 [NS]		
	Elemental nutrition vs. NI			
6 mo	NR[50]	**Elemental nutrition vs. NI**		
12 mo	NR[50]			
18 mo	NR[50]	p=0.19 [NS]		
24 mo	NR[50]	p=0.17 [NS]		
		p=0.04 [SS]		
		p=0.03 [SS]		
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	NR[55]	NR	1 [NA]	Inconclusive

95% CI=95 percent confidence interval; mo=month(s); MP=mercaptopurine; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias; SS=statistically significant

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

£ Calculated

Table 8: Proportion of patients maintaining remission¥ (n/N) – Non-randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	10/21 (47.6) vs. 4/18 (22.2)[56]	p=0.0003 [SS] RR=2.14 (0.81, 5.67), p=0.18 [NS][£]	1 [high ROB]	Inconclusive
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
12 mo	19/20 (95.0) vs. 13/20 (65.0)[30]	p=NR RR=1.46 (1.04, 2.05)[£]	2 [high ROB]	In favour of elemental nutrition
12 mo	15/20 (75.0) vs. 7/20 (35.0)[57]	p=0.01 [SS] RR=2.14 (1.12, 4.10)[£]		
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	No evidence
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	25/32 (78.1) vs. 16/24 (66.6)[58]	p=0.51 [NS] RR=1.17 (0.83, 1.64)[£]	1 [high ROB]	Inconclusive

95% CI=95 percent confidence interval; CDAI=crohn's disease activity index; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias; SS=statistically significant

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated
[β] Sulfasalazine (3g/d) or prednisolone (10mg/d)
[µ] Infliximab (5 mg/kg)
¥ Remission defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria additionally)

Table 9: Cumulative survival rate for being in remission (%) – Non-randomised controlled trials

Follow-up	Arm-specific Kaplan-Meier survival rate estimates	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[56]	NR	1 [NA]	No evidence
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
6, 12, 60 mo	NR[30]	NR	1 [NA]	No evidence
12 mo	NR[57]	p=0.01 [SS] in favour of elemental nutrition as reported	1 [high ROB]	Inconclusive
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug$^{\beta}$ (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12 mo 24 mo 48 mo	94% (NR) vs. 75% (NR) vs. 63% (NR) vs. 50% (NR)[51] 63% (NR) vs. 66% (NR) vs. 42% (NR) vs. 33% (NR)[51] 63% (NR) vs. 66% (NR) vs. 0% (NR) vs. 0% (NR)[51]	**At 48 mo** p<0.05 [1 vs. 3] SS p<0.01 [1 vs. 4] SS p<0.05 [2 vs. 3] SS p<0.05 [2 vs. 4] SS p≥0.05 [1 vs. 2] NS	1 [high ROB]	Inconclusive
Elemental nutrition/Drug$^{\mu}$ (restricted diet) vs. Drug$^{\mu}$ (unrestricted diet)				
14 mo	NR[58]	p=0.32 [NS]	1 [high ROB]	Inconclusive

95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias; SS=statistically significant

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

$^{£}$ Calculated

$^{\beta}$ Sulfasalazine (3g/d) or prednisolone (10mg/d)

$^{\mu}$ Infliximab (5 mg/kg)

4.4.2 Development of Relapse/Recurrence

In seven of the eight included trials, the development of relapse/recurrence was reported as the proportion of patients developing relapse[30, 50, 52, 55-58] and/or mean time to relapse.[56] All seven studies reported clinical relapse (defined using CDAI alone or with other criteria) and one study[30] additionally reported endoscopic relapse (Rutgeerts score≥2). See Table 10 and Table 11.

Elemental nutrition vs. No intervention (i.e., unrestricted/free diet)

Randomised controlled trials

Our meta-analysis of two RCTs[50, 52] indicated a significantly reduced risk of relapse amongst participants receiving elemental nutrition vs. no intervention at 12 to 24 months of follow-up (pooled RR=0.57, 95% CI: 0.38, 0.84; Chi^2=0.04, p=0.83, I^2=0%). See Figure 4 and Table 10.

Figure 4: Patients developing relapse/recurrence at 12 to 24 months: elemental nutrition vs. no intervention (unrestricted diet)

Non-randomised controlled trials

Findings from three trials consistently showed a significant benefit of elemental nutrition vs. no intervention in reducing risk of clinical (RR=0.50, 95% CI: 0.25, 0.98;[56] RR=0.14, 95% CI: 0.02, 1.00;[30] and RR=0.38, 95% CI: 0.16, 0.87[57]) as well as endoscopic relapse (RR=0.42, 95% CI: 0.20, 0.88)[30] at 12 months post-baseline. In one of the trials,[30] the between-group difference in the risk of endoscopic relapse at 60 months follow-up was not statistically significant (RR=0.68, 95% CI: 0.42, 1.11) [review conclusion: inconclusive]. See Table 11.

In one trial,[56] at 12 months post-baseline, the mean time (in months) to relapse in the elemental nutrition group was significantly longer compared to no intervention group (7.4 vs. 6.2, mean difference: 1.20, 95% CI: 0.35, 2.04). See Table 12.

Elemental nutrition vs. Drug

Randomised controlled trials

In one trial,[50] the difference in the occurrence of relapse between participants receiving elemental nutrition and 6-MP after 24 months of follow-up was not statistically significant (RR=1.61, 95% CI: 0.73, 3.53) [review conclusion: inconclusive]. See Table 10.

Non-randomised controlled trials

Evidence not reported.[51] See Table 11.

Elemental nutrition vs. Elemental nutrition plus drug

Randomised controlled trials

No trial with these comparisons.

Non-randomised controlled trials

Evidence not reported.[51] See Table 11.

Elemental nutrition plus drug vs. Drug

Randomised controlled trials

No trial with these comparisons.

Non-randomised controlled trials

Of the two available trials with the above-mentioned comparisons,[51, 58] only one reported this outcome.[58] In this trial, the difference in the occurrence of relapse between participants receiving elemental nutrition plus infliximab vs. infliximab alone was not statistically significant (RR=0.65, 95% CI: 0.27, 1.56) [review conclusion: inconclusive]. See Table 11.

Elemental nutrition vs. Polymeric nutrition

Randomised controlled trials

In one trial,[55] at 12 months of follow-up, the difference in the occurrence of relapse between participants receiving elemental and polymeric nutrition was not statistically significant (RR=1.18, 95% CI: 0.48, 2.83) [review conclusion: inconclusive]. See Table 10.

Non-randomised controlled trials

No trial with these comparisons.

Table 10: Proportion of patients developing relapse/recurrence¥ (n/N) – Randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	9/26 (34.6) vs. 16/25 (64.0)[52] (relapse: CDAI plus other criteria)	HR=0.40 (0.16, 0.98) adjusted estimate RR=0.54 (0.29, 0.99)[£]	1 [low ROB]	In favour of elemental nutrition group
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
24 mo	**Elemental nutrition vs. 6-MP** 12/32 (37.5) vs. 7/30 (23.3)[50] (relapse: CDAI plus other criteria)	**Elemental nutrition vs. 6-MP** RR=1.61 (0.73, 3.53)[£]	1 [low ROB]	Inconclusive (elemental nutrition vs. 6-MP)
24 mo	**Elemental nutrition vs. NI** 12/32 (37.5) vs. 21/33 (63.6)[50] (relapse: CDAI plus other criteria)	**Elemental nutrition vs. NI** RR=0.58 (0.35, 0.98)[£]		In favour of elemental nutrition group (vs. NI)
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	8/19 (42.1) vs. 5/14 (35.7)[55]	p=NR [NS] RR=1.18 (0.48, 2.83)[£]	1 [high ROB]	Inconclusive

95% CI=95 percent confidence interval; CDAI=crohn's disease activity index; HR=hazard ratio; mo=month(s); MP=mercaptopurine; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated
[¥] Relapse defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria in addition

Table 11: Proportion of patients developing relapse/recurrence¥ (n/N) – Non-randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	7/21 (33.3) vs. 14/18 (77.7)[56] (relapse: CDAI plus other criteria)	p<0.00001 [SS] RR=0.50 (0.25, 0.98)[£]	1 [unclear ROB]	In favour of elemental nutrition
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
	Clinical relapse (CDAI≥150/200)	**Clinical relapse (12 mo)**	1 [high ROB]	**Clinical relapse**
12 mo	1/20 (5.0) vs. 7/20 (35.0)[30]	p=0.048 [SS]		In favour of elemental nutrition (at 12 mo)
60 mo	6/20 (30.0) vs. 12/20 (60.0)[30]	RR=0.14 (0.02, 1.00)[£]		
		Clinical relapse (60 mo)		Inconclusive (at 60 mo)
		p=0.11 [NS]		
		RR=0.50 (0.23, 1.07)[£]		
	Endoscopic relapse (Rutgeerts score≥2)	**Endoscopic relapse (6 mo)**	1 [low ROB]	**Endoscopic relapse**
6 mo	5/20 (25.0) vs. 8/20 (40.0)[30]	p=0.50 [NS]		In favour of elemental nutrition (12 mo)
12 mo	6/20 (30.0) vs. 14/20 (70.0)[30]	RR=0.62 (0.24, 1.58)[£]		
60 mo	9/16 (56.2) vs. 14/17 (82.3)[30]	**Endoscopic relapse (12 mo)**		Inconclusive (at 6 mo and 60 mo)
		p=0.027 [SS]		
		RR=0.42 (0.20, 0.88)[£]		
		Endoscopic relapse (60 mo)		
		p=0.21 [NS]		
		RR=0.68 (0.42, 1.11)[£]		
12 mo	5/20 (25.0) vs. 13/20 (65.0)[57]	OR=0.20 (0.04, 0.70), p=0.03[£] RR=0.38 (0.16, 0.87)[£]	1 [high ROB]	In favour of elemental nutrition
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	Inconclusive
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	7/32 (21.8) vs. 8/24 (33.3)[58]	p=0.51 [NS] RR=0.65 (0.27, 1.56)[£]	1 [high ROB]	Inconclusive

95% CI=95 percent confidence interval; CDAI=crohn's disease activity index; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias; SS=statistically significant

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive; ** Decision was consensus-based

[£] Calculated; [β] Sulfasalazine (3g/d) or prednisolone (10mg/d) [µ] Infliximab (5 mg/kg)

¥ Relapse defined using CDAI only unless specified otherwise (e.g., endoscopic, blood parameter, other criteria additionally)

Table 12: Time to relapse/recurrence (mean # of months) – Non-randomised controlled trials

Follow-up	Arm-specific estimates Mean (SD or 95% CI)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	7.4 (0.9) vs. 6.2 (0.4)[56]	p=NR MD=1.20 (0.35, 2.04), p=0.012[£]	1 [unclear ROB]	In favour of elemental nutrition
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
6, 12, 60 mo	NR[30]	NR	1 [NA]	No evidence
12 mo	NR[57]	NR	1 [NA]	No evidence
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	No evidence
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	NR[58]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; RCT=randomised controlled trial; RR=risk ratio (relative risk); SD=standard deviation; SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

[£] Calculated

[β] Sulfasalazine (3g/d) or prednisolone (10mg/d)

[µ] Infliximab (5 mg/kg)

4.4.3 Incidence of Mucosal Healing (Endoscopic Remission)

Only one of the eight included trials (non-randomised study)[57] reported this outcome, which was based on mucosal inflammation grade categorized as follows: 0=macroscopically normal, 1= granular mucosa and contact bleeding, 2= erythematous and oedematous mucosa, aphtoid or superficial ulcers, and 3=deep ulcers with slough and inflammatory pseudo polyps. In this non-randomised study, at 12 months of follow-up, the proportion of participants achieving grade 0 between elemental nutrition and no intervention (unrestricted diet) groups was not significantly different (RR=2.70, 95% CI: 0.62, 11.72) [review conclusion: inconclusive]. See Table 13.

Table 13: Proportion of patients with mucosal healing (n/N) – Non-randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[56]	NR	1 [NA]	No evidence
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
6, 12, 60 mo	NR[30]	NR	1 [NA]	No evidence
12 mo	6/20 (30.0) vs. 2/18 (11.1)[57] (Grade 0: macroscopically normal)	p=NR RR=2.70 (0.62, 11.72)[£]	1 [low ROB]	Inconclusive
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	No evidence
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	NR[58]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; RCT=randomised controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated
[β] Sulfasalazine (3g/d) or prednisolone (10mg/d)
[µ] Infliximab (5 mg/kg)

4.4.4 Need for Surgery

Three of the eight included trials reported this outcome: one RCT[50] and two non-RCTs.[30, 57] See Table 14 and Table 15.

Elemental nutrition vs. No intervention (i.e., unrestricted/free diet)

Randomised controlled trials

At 24 months follow-up,[50] the proportion of participants in need of surgery was not statistically significantly different between the elemental nutrition and no intervention groups (RR=1.03, 95% CI: 0.06, 15.79; Fisher's exact test p>0.99) [review conclusion: inconclusive]. See Table 14.

Non-randomised controlled trials

In two trials,[30, 57] at 12 to 60 months of follow-up, the difference in proportion of participants in need of surgery between the elemental nutrition and no intervention groups was not statistically significant (RR=0.20, 95% CI: 0.02, 1.56) [review conclusion: inconclusive]. See Table 15.

Elemental nutrition vs. Drug

Randomised controlled trials

At 24 months follow-up,[50] the difference in proportion of participants in need of surgery between the elemental nutrition and 6-MP groups was not statistically significant (RR=0.93, 95% CI: 0.06, 14.32; Fisher's exact test p>0.99) [review conclusion: inconclusive]. See Table 14.

Non-randomised controlled trials

Evidence not reported.[51] See Table 15.

Table 14: Proportion of patients in need of surgery (n/N) – Randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[52]	NR	1 [NA]	No evidence
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
24 mo	**Elemental nutrition vs. 6-MP** 1/32 (3.1) vs. 1/30 (3.1)[50]	**Elemental nutrition vs. 6-MP** p>0.99 [NS] Fisher's exact test[£] RR=0.93 (0.06, 14.32)[£]	1 [low ROB]	Inconclusive
24 mo	**Elemental nutrition vs. NI** 1/32 (3.1) vs. 1/33 (3.0)[50]	**Elemental nutrition vs. NI** p>0.99 [NS] Fisher's exact test[£] RR=1.03 (0.06, 15.79)[£]		
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	NR[55]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; mo=month(s); MP=Mercaptopurine; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; RR=risk ratio (relative risk); ROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

[£] Calculated

Table 15: Proportion of patients in need of surgery (n/N) – Non-randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[56]	NR	1 [NA]	Inconclusive
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
60 mo	1/20 (5.0) vs. 5/20 (25.0)[30]	p=0.18 [NS] RR=0.20 (0.02, 1.56)[£]	2 [low ROB]	Inconclusive
12 mo	0/20 (0.0) vs. 2/20 (10.0)[57]	p=NR		
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	Inconclusive
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	NR[58]	NR	1 [NA]	No evidence

RR=risk ratio (relative risk); SROB=summary risk of bias; SD=standard deviation; 95% CI=95 percent confidence interval; NR=not reported; mo=month(s); NA=not applicable; NI=no intervention

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated
[β] Sulfasalazine (3g/d) or prednisolone (10mg/d)
[µ] Infliximab (5 mg/kg)

4.4.5 Adherence

Seven of the eight included trials reported any information on adherence: two RCTs[52, 55] and five non-RCTs.[30, 51, 56-58] See Table 16 and Table 17.

Elemental nutrition vs. No intervention (i.e., unrestricted/free or restricted diet)

Randomised controlled trials

In one RCT,[52] the difference in the rates of adherence at 12 months of follow-up between the groups of elemental nutrition and no intervention (unrestricted diet) was not statistically significant (77% vs. 80%; RR=0.96, 95% CI: 0.72, 1.28) [review conclusion: inconclusive]. See Table 16.

Non-randomised controlled trials

The rate of adherence reported for two trials[30, 56] was significantly lower in the elemental nutrition vs. no intervention group at 12 months (RR=0.81, 95% CI: 0.65, 0.99)[56] and 60 months (RR=0.80, 95% CI: 0.64, 0.99)[30] after the baseline. For the remaining two trials comparing elemental nutrition to no intervention (unrestricted diet[57] or restricted diet,[51]) the between group differences in adherence were not statistically significant at 12 months (90% vs. 100%, Fisher's exact test p=0.48)[57] and 48 months post-baseline (88% vs. 100%, Fisher's exact test p>0.99)[51] [review conclusion: inconclusive]. See Table 17.

Elemental nutrition vs. Drug

Randomised controlled trials

No evidence reported.[50]

Non-randomised controlled trials

In one trial comparing elemental nutrition to sulfasalazine/prednisolone,[51] the between group differences in adherence at 48 months post-baseline were not statistically significant (88% vs. 100%, Fisher's exact test p=0.84) [review conclusion: inconclusive]. See Table 17.

Elemental nutrition vs. Elemental nutrition plus drug

Randomised controlled trials

No trial with these comparisons

Non-randomised controlled trials

In one trial comparing the elemental nutrition to the combination of elemental nutrition and sulfasalazine/prednisolone,[51] the between group differences in adherence at 48 months post-baseline

were not statistically significant (88% vs. 77.3%, Fisher's exact test p=0.55) [review conclusion: inconclusive]. See Table 17.

Elemental nutrition plus drug vs. Drug

Randomised controlled trials

No trial with these comparisons

Non-randomised controlled trials

In one trial comparing the combination of elemental nutrition and sulfasalazine/prednisolone to sulfasalazine/prednisolone alone,[51] the between group differences in adherence at 48 months post-baseline were not statistically significant (77.3% vs. 100%, Fisher's exact test p=0.37). Another trial comparing the combination of elemental nutrition and infliximab vs. infliximab alone[58] reported 78% of adherence for the elemental nutrition group. No data was reported for the infliximab group [review conclusion: inconclusive]. See Table 17.

Elemental nutrition vs. Polymeric nutrition

Randomised controlled trials

The rate of adherence reported in one trial[55] was significantly lower in the elemental nutrition vs. polymeric nutrition group at 12 months after the baseline (68.4% vs. 100%, RR=0.68, 95% CI: 0.50, 0.92). See Table 16.

Non-randomised controlled trials

No trial with these comparisons.

Table 16: Proportion of patients with adherence (n/N) – Randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	20/26 (77.0) vs. 20/25 (80.0)[52]	RR=0.96 (0.72, 1.28)[£]	1 [low ROB]	Inconclusive
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
24 mo	NR[50]	NR	1 [NA]	No evidence
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	13/19 (68.4) vs. 14/14 (100.0)[55]	RR=0.68 (0.50, 0.92)[£]	1 [unclear ROB]	In favour of polymeric nutrition group

95% CI=95 percent confidence interval; MP=Mercaptopurine; NI=no intervention; NR=not reported; RCT=randomised controlled trial; RR=risk ratio (relative risk); SD=standard deviation; SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated

Table 17: Proportion of patients with adherence (n/N) – Non-randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	17/21 (80.9) vs. 18/18 (100.0)[56]	p=NR RR=0.81 (0.65, 0.99)[£]	1 [unclear ROB]	In favour of NI group
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
12 mo 60 mo	20/20 (100.0) vs. 20/20 (100.0)[30] 16/20 (80.0) vs. 20/20 (100.0)[30]	p=NR RR=0.80 (0.64, 0.99)[£]	2 [low ROB]	In favour of the NI (60 mo)
12 mo	18/20 (90.0) vs. 20/20 (100.0)[57]	p=0.48 Fisher's exact test[£] NS		Inconclusive
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
48 mo	22/25 (88.0) vs. 17/22 (77.3) vs. 8/8 (100.0) vs. 6/6 (100.0)[51]	Fisher's exact test[£] p=0.55 [1 vs. 2] NS p=0.84 [1 vs. 3] NS p>0.99 [1 vs. 4] NS p=0.37 [2 vs. 3] NS p=0.53 [2 vs. 4] NS	1 [low ROB]	Inconclusive
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	25/32 (78.1) vs. NR (NR)[58]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; RR=risk ratio (relative risk); SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

[£] Calculated

[β] Sulfasalazine (3g/d) or prednisolone (10mg/d)

[µ] Infliximab (5 mg/kg)

4.4.6 Withdrawal from Steroids

Two of the eight included trials (one RCT[55] and one non-RCT[56]) reported the proportion of participants who withdrew from taking steroids. Results from both trials showed statistically non-significant differences in the withdrawals from steroids at 12 months post-baseline between the groups of elemental nutrition vs. polymeric nutrition (42.1% vs. 42.8%, RR=0.98, 95% CI: 0.44, 2.19)[55] or no intervention – unrestricted diet (23.8% vs. 22.2%, RR=1.07, 95% CI: 0.33, 3.39)[56] [review conclusion: inconclusive]. See Table 18 and Table 19.

Table 18: Proportion of patients who withdrew from taking steroids (n/N) – Randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[52]	NR	1 [NA]	No evidence
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
24 mo	NR[50]	NR	1 [NA]	No evidence
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	8/19 (42.1) vs. 6/14 (42.8)[55]	p=NR [NS] RR=0.98 (0.44, 2.19)[£]	1 [unclear ROB]	Inconclusive

95% CI=95 percent confidence interval; mo=month(s); MP=Mercaptopurine; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RR=risk ratio (relative risk); SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated

Table 19: Proportion of patients who withdrew from taking steroids (n/N) – Non-randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	5/21 (23.8) vs. 4/18 (22.2)[56]	p=NR RR=1.07 (0.33, 3.39)[£]	1 [unclear ROB]	Inconclusive
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
6, 12, 60 mo	NR[30]	NR	1 [NA]	No evidence
12 mo	NR[57]	NR	1 [NA]	No evidence
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	No evidence
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	NR[58]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; RCT=randomised controlled trial; SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

[£] Calculated

[β] Sulfasalazine (3g/d) or prednisolone (10mg/d)

[µ] Infliximab (5 mg/kg)

4.4.7 Steroid Dose Tapering

Only one trial (non-RCT) reported this outcome.[56] At 12 months of follow-up, the difference in the proportion of participants whose steroid dose was tapered in those receiving elemental nutrition vs. no intervention (unrestricted diet) was not statistically significant (47.6% vs. 22.2%, RR=2.14, 95% CI: 0.80, 5.67) [review conclusion: inconclusive]. See Table 20.

Table 20: Proportion of patients whose steroid dose was tapered (n/N) – Non-randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	10/21 (47.6) vs. 4/18 (22.2)[56]	p=NR RR=2.14 (0.80, 5.67)[£]	1 [unclear ROB]	Inconclusive
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
6, 12, 60 mo	NR[30]	NR	1 [NA]	No evidence
12 mo	NR[57]	NR	1 [NA]	No evidence
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug[β] (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	No evidence
Elemental nutrition/Drug[µ] (restricted diet) vs. Drug[µ] (unrestricted diet)				
14 mo	NR[58]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; RCT=randomised controlled trial; SROB=summary risk of bias

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
[£] Calculated
[β] Sulfasalazine (3g/d) or prednisolone (10mg/d)
[µ] Infliximab (5 mg/kg)

4.4.8 Crohn's Disease Activity Index

Two non-RCTs[57, 58] reported incomplete data on 12-14 month post-treatment mean CDAI score (missing study group-specific means and variability parameters) showing significantly lower mean disease activity in favour of the elemental nutrition vs. no intervention (unrestricted diet) group (p=0.04)[57] and non-significant difference between the groups of elemental nutrition plus infliximab vs. infliximab alone (p>0.05)[58] [review conclusion: inconclusive]. See Table 21.

Table 21: Crohn's Disease Activity Index (score: 0-600) – Non-randomised controlled trials

Follow-up	Arm-specific estimates Mean (SD or 95% CI)	Difference (p value or 95% CI)	# of non-RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (unrestricted diet) vs. NI (unrestricted diet)				
12 mo	NR[56]	NR	1 [NA]	No evidence
Elemental nutrition (restricted diet) vs. NI (unrestricted diet)				
6, 12, 60 mo	NR[30]	NR	1 [NA]	No evidence
12 mo	NR[57]	p=0.04 [SS] in favour of elemental nutrition group	1 [high ROB]	Inconclusive
Elemental nutrition (restricted diet) vs. Elemental nutrition/Drug$^{\beta}$ (restricted diet) vs. Drug (restricted diet) vs. NI (restricted diet)				
12, 24, 48 mo	NR[51]	NR	1 [NA]	No evidence
Elemental nutrition/Drug$^{\mu}$ (restricted diet) vs. Drug$^{\mu}$ (unrestricted diet)				
14 mo	NR[58]	p>0.05 [NS]	1 [high ROB]	Inconclusive

95% CI=95 percent confidence interval; mo=month(s); NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; SD=standard deviation; SROB=summary risk of bias; SS=statistically significant

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

$^{\varepsilon}$ Calculated

$^{\beta}$ Sulfasalazine (3g/d) or prednisolone (10mg/d)

$^{\mu}$ Infliximab (5 mg/kg)

4.4.9 Health Related Quality of Life

Only one trial (RCT)[52] reported any information on health related quality of life. At 12 month of follow-up, the adjusted mean Inflammatory Bowel Disease Questionnaire (IBDQ) score did not differ between the participants receiving elemental nutrition vs. no intervention unrestricted diet (171.9 vs. 176.7, p>0.05). See Table 22.

Table 22: Health-related quality of life (mean IBDQ score; score range: 32-224) – Randomised controlled trials

Follow-up	Arm-specific estimates Mean (SD or 95% CI)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	171.9 (126.4, 217.3) vs. 176.7 (142.5, 211.0)[52]	Adjusted mean IBDQ score difference p>0.05 [NS]	1 [high ROB]	No difference
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
24 mo	NR[50]	NR	1 [NA]	No evidence
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	NR[55]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; mo=month(s); MP=mercaptopurine; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; SD=standard deviation; SROB=summary risk of bias; IBDQ= Inflammatory Bowel Disease Questionnaire

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
£ Calculated

4.4.10 Adverse Events and Complications

For two RCTs reporting adverse events,[50, 52] no meaningful comparison was possible, since the effect estimates could not be generated due to zero counts in the nominators [review conclusion: inconclusive]. For example, one trial reported the absence of adverse events.[52] In the other trial,[50] none of the 32 participants in the elemental nutrition group experienced any adverse event or complication. Of the 30 participants in the 6-MP group, two experienced elevated aspartate transaminase (AST), one participant- hair loss, and one participant – abscess (complication). Of the 33 participants in the no intervention group (unrestricted diet), one experienced elevated amylase. None of the participants in this group experienced any complication. See Table 23 and Table 24.

Table 23: Proportion of patients with adverse event(s) (n/N) – Randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	0/26 (0.0) vs. 0/25 (0.0)[52]		1 [low ROB]	Inconclusive
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
24 mo	**Elemental nutrition vs. 6-MP** 0/32 (0.0) vs. 2/30 (6.6) [elevated AST] and 1/30 (3.1) [hair loss][50] **Elemental nutrition vs. NI** 0/32 (0.0) vs. 1/33 (3.0) [elevated amylase][50]	**Elemental nutrition vs. 6-MP** - **Elemental nutrition vs. NI**	1 [low ROB]	Inconclusive
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	NR[55]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; AST=aspartate transaminase; mo=month(s); MP=mercaptopurine; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; SROB=summary risk of bias; SS=statistically significant

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive
** Decision was consensus-based
£ Calculated

Table 24: Proportion of patients with complication(s) (n/N) – Randomised controlled trials

Follow-up	Arm-specific estimates n/N (%)	Difference (p value or 95% CI)	# of RCTs [SROB across studies]**	Treatment effect Conclusion*
Elemental nutrition (with unrestricted diet) vs. NI (unrestricted diet)				
12 mo	0/26 (0.0) vs. 0/25 (0.0)[52]		1 [low ROB]	Inconclusive
Elemental nutrition (with restricted diet) vs. 6-MP (with unrestricted diet) vs. NI (unrestricted diet)				
24 mo	**Elemental nutrition vs. 6-MP** 0/32 (0.0) vs. 1/30 (3.1) [abscess] [50] **Elemental nutrition vs. NI** 0/32 (0.0) vs. 0/33 (3.0)[50]	**Elemental nutrition vs. 6-MP** **Elemental nutrition vs. NI**	1 [low ROB]	Inconclusive
Elemental nutrition (with unrestricted diet) vs. Polymeric nutrition (with unrestricted diet)				
12 mo	NR[55]	NR	1 [NA]	No evidence

95% CI=95 percent confidence interval; mo=month(s); MP=mercaptopurine; NA=not applicable; NI=no intervention; NR=not reported; NS=statistically not significant; RCT=randomised controlled trial; SROB=summary risk of bias; SS=statistically significant

* Favours elemental nutrition (or comparator treatment), no difference, or inconclusive

** Decision was consensus-based

£ Calculated

4.4.11 Unreported Outcomes of Interest

None of the eight included trials reported changes in anthropometric measures (e.g., weight, BMI, height, linear growth) and pubertal development.

4.5 Cost-effectiveness of elemental diet

This review did not identify any study assessing cost-effectiveness of elemental nutrition. One RCT[52, 54] reported monthly costs for the two study groups of elemental nutrition and no intervention (i.e., free diet). This study was not an economic evaluation; therefore no formal assessment of methodological quality of economic assessment was undertaken. In addition there was not sufficient information on the cost data collection and analysis. According to this study report,[54] the adjusted one year monthly cost treatments were not significantly different between the elemental nutrition and free diet groups (US$ 880.00 vs. US$ 600.00, p>0.05). See Cost Table in Appendix IV.

4.6 Rating the overall quality of evidence (GRADE System)

The overall quality ratings for each gradable outcome (i.e., maintenance of remission, risk of relapse, mucosal healing, need of surgery, withdrawal from steroids, steroid dose tapering, adherence, and adverse events) are presented in the Evidence Profile (EP) Table (see Table 25).

The overall quality of evidence for each gradable outcome was rated for the comparison between elemental nutrition and no intervention, given that two RCTs[50, 52] comparing elemental nutrition to no intervention (unrestricted diet) were judged to be the only potentially combinable evidence.

The overall quality ratings across the gradable outcomes for the above-mentioned comparison were as follows: maintenance of remission (Grade: Very Low), risk of relapse (Grade: High), need of surgery (Grade: Very Low), adherence (Grade: Very Low), and adverse events (Grade: Moderate). Mucosal healing, withdrawal from steroids, and steroid dose tapering were not rated due to the absence of evidence.

Table 25: GRADE evidence profile for gradable outcomes reported in RCTs of Crohn's disease
(adapted from Guyatt et al., 2011)[49]

Outcome [follow-up timing]	N of studies reporting outcome (participants)	Pooled effect estimate (95% CI) and conclusion	SROB across studies	Consistency	Directness	Precision	Outcome reporting bias	Quality of the evidence (GRADE)*
Elemental nutrition vs. NI (i.e., unrestricted/free diet) – 2 RCTs[50, 52]								
Maintenance of remission [12 mo]	1 (65)[50]	No pooled estimate RR=1.37 (0.86, 2.17) **Inconclusive**	High SROB	NA	Direct	Imprecise	Likely	Very low
Maintenance of remission [24 mo]	1 (65)[50]	No pooled estimate RR=2.06 (1.00, 4.43) **In favour of elemental nutrition**	High SROB	NA	Direct	Precise	Likely	Very low
Development of relapse/recurrence [12 mo-24 mo]	2 (116)[50, 52]	Pooled estimate RR=0.57 (0.38, 0.84) **In favour of elemental nutrition**	Low SROB	Consistent	Direct	Precise	Unlikely	High
Mucosal healing [NA]	0 (0)	NA	NA	NA	NA	NA	NA	NA (no evidence)
Need of surgery [24 mo]	1 (65)[50]	No pooled estimate RR=1.03 (0.06, 15.79) **Inconclusive**	Low SROB	NA	Direct	Imprecise	Likely	Very low
Withdrawal from steroids [NA]	0 (0)	NA	NA	NA	NA	NA	NA	NA (no evidence)
Steroid dose tapering [NA]	0 (0)	NA	NA	NA	NA	NA	NA	NA (no evidence)
Adherence [12 mo]	1 (51)[52]	No pooled estimate RR=0.96 (0.72, 1.28) **Inconclusive**	Low SROB	NA	Direct	Imprecise	Likely	Very low
Adverse events [12 mo-24 mo]	2 (116)[50, 52]	No pooled estimate Parameters not estimable **Inconclusive**	Low SROB	Consistent	Direct	Imprecise	Unlikely	Moderate

GRADE= Grading of Recommendations, Assessment, Development, and Evaluation; RCT=randomised controlled trial; CI=confidence interval; SROB=summary risk of bias; RCT=randomised controlled trial; NA=not applicable; mo(s)=month(s); NI=no intervention

*GRADE categories: high, moderate, low, very low, NA (no evidence)

4.7 Summary of Findings

Limited evidence from two RCTs in patients with CD in remission[50, 52] has indicated a significant beneficial effect of elemental nutrition vs. no intervention (unrestricted diet) in maintaining remission after 24 months of follow-up (RR=2.06, 95% CI: 1.00, 4.43; very low grade evidence[50]) and preventing the occurrence of relapse at 12-24 months of follow-up (pooled RR=0.57, 95% CI: 0.38, 0.84; high grade evidence[50, 52]). The shorter-term maintenance rate of remission (at 6 and 12 months) between the two randomised groups was not significantly different (12 month RR=1.37, 95% CI: 0.86, 2.17; very low grade evidence; inconclusive result due to wide 95% CIs).[50]

Similarly, three non-RCTs also showed significant benefits of elemental nutrition over no intervention (unrestricted diet) in maintaining remission at 12-48 months[30, 57] and preventing the occurrence of relapse at 12 months.[30, 56, 57] Evidence on the maintenance of remission from two non-RCTs was rendered inconclusive due to wide non-significant 95% CIs (RR=2.14, 95% CI: 0.81, 5.67)[56] and missing data (i.e., effect estimates and/or 95% CIs).[51] In one non-RCT,[56] the use of elemental nutrition was associated with a significantly longer time to relapse compared to no intervention after 12 months of follow-up (MD=1.20, 95% CI: 0.35, 2.04).

According to one non-RCT,[57] the incidence of mucosal healing (endoscopic remission) at 12 months between patients receiving elemental nutrition vs. no intervention (unrestricted diet) was not significantly different (inconclusive results; RR=2.70, 95% CI: 0.62, 11.72).

Based on evidence from two non-RCTs,[30, 56] and one RCT,[55] there was a significantly worse adherence rate in the elemental nutrition groups compared to either no intervention (unrestricted diet)[30, 56] or polymeric nutrition group (RR=0.68, 95% CI: 0.50, 0.92).[55]

In general, evidence comparing the effects of elemental nutrition and active treatment(s) (sulfasalazine/prednisolone, infliximab, elemental nutrition, polymeric nutrition, or combination) across the outcomes of interest yielded statistically non-significant results with wide 95% CIs implying possible moderate to large effect size treatment effects in both directions compatible both with benefit and harm from elemental nutrition (inconclusive results).

Evidence on complications and adverse events was too sparse (e.g., zero events, low counts) to derive effect estimates and 95% CIs and permit any meaningful comparison between the treatments.

There was no reported evidence on changes in anthropometric measures (e.g., body weight, height, BMI, linear growth rate) and pubertal development. See Table 26.

Table 26: Summary of findings and overall quality ratings of evidence regarding the differences between elemental nutrition and other interventions for each reported outcome

Conclusive evidence suggesting difference	Conclusive evidence suggesting no difference	Inconclusive evidence
Maintenance of Remission (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
At 24 months 1 RCT[50] [very low grade] **In favour of elemental nutrition** At 12-48 months 2 non-RCTs[30, 57] **In favour of elemental nutrition**	None	At 6 and 12 months (NS) 1 RCT[50] [very low grade] At 12 months (NS) 1 non-RCT[56] At 48 months (SS=favoured elemental nutrition) 1 non-RCT[51]
Elemental Nutrition vs. Drug[50, 51]		
None	None	At 6, 12, 24 months (NS) 1 RCT[50] At 48 months (SS=favoured elemental nutrition) 1 non-RCT[51]
Elemental Nutrition vs. Elemental Nutrition plus Drug[51]		
None	None	At 48 months (NS) 1 non-RCT[51]
Elemental Nutrition plus Drug vs. Drug[51, 58]		
None	None	At 14 months (NS) 1 non-RCT[58] At 48 months (SS=favoured elemental nutrition plus drug) 1 non-RCT[51]
Elemental Nutrition vs. Polymeric Nutrition[55]		
None	None	At 12 months (NS) 1 RCT[55]
Risk of Relapse/Recurrence (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
At 12-24 months	None	At 60 months (NS)

2 RCTs[50, 52] [high grade] – pooled estimate **In favour of elemental nutrition** At 12 months 3 non-RCTs[30, 56, 57] **In favour of elemental nutrition**		1 non-RCT[30]
Elemental Nutrition vs. Drug[50, 51]		
None	None	At 24 months (NS) 1 RCT[50]
Elemental Nutrition plus Drug vs. Drug[51, 58]		
None	None	At 14 months (NS) 1 non-RCT[58]
Elemental Nutrition vs. Polymeric Nutrition[55]		
None	None	At 12 months (NS) 1 RCT[55]
Time To Relapse (# of months)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
At 12 months 1 non-RCT[56] **In favour of elemental nutrition**	None	None
Mucosal Healing (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
None	None	At 12 months (NS) 1 non-RCT[57]
Need for Surgery (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
None	None	At 24 months (NS) 1 RCT[50] [very low grade] At 12 and 60 months (NS) 2 non-RCTs[30, 57]
Elemental Nutrition vs. Drug[50, 51]		
None	None	At 24 months (NS) 1 RCT[50]
Adherence (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
At 12 and 60 months	None	At 12 months (NS)

2 non-RCTs[30, 56] **In favour of no intervention**		1 RCT[52] [very low grade] At 12 and 48 months (NS) 2 non-RCTs[51, 57]
Elemental Nutrition vs. Drug[50, 51]		
None	None	At 48 months (NS) 1 non-RCT[51]
Elemental Nutrition vs. Elemental Nutrition plus Drug[51]		
None	None	At 48 months (NS) 1 non-RCT[51]
Elemental Nutrition plus Drug vs. Drug[51, 58]		
None	None	At 48 months (NS) 1 non-RCT[51]
Elemental Nutrition vs. Polymeric Nutrition[55]		
At 12 months 1 RCT[55] **In favour of polymeric nutrition**	None	None
Withdrawal from Steroids (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
None	None	At 12 months (NS) 1 non-RCT[56]
Elemental Nutrition vs. Polymeric Nutrition[55]		
None	None	At 12 months (NS) 1 RCT[55]
Steroid Dose Tapering (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
None	None	At 12 months (NS) 1 non-RCT[56]
Health Related Quality of Life (mean IBDQ score)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
None	At 12 months (NS) 1 RCT[52] **In no favour of either intervention**	None
Adverse Events and Complications (n/N)		
Elemental Nutrition vs. No Intervention[30, 50-52, 56, 57]		
None	None	At 12 and 24 months (estimates could not be generated)

		2 RCTs[50, 52] [moderate grade]
Elemental Nutrition vs. Drug[50, 51]		
None	None	At 24 months (estimate could not be generated) 1 RCT[50]
NS=statistically not significant; RCT=randomised controlled trial; SS=statistically significant		

4.8 Other Analyses

4.8.1 Publication bias

The impact of publication bias on the pooled treatment effect estimates (i.e., degree of funnel plot asymmetry) could not be explored due to an insufficient number of data points in the forest/funnel plots.

4.8.2 Subgroup effects

The reviewed evidence was too sparse and heterogeneous to allow exploration of whether or not the relative effect of elemental nutrition differed by study-level methodological (i.e., risk of bias, type of data analysis) or patient-related characteristics (i.e., age, sex, or induction therapy).

5 DISCUSSION

CD is a chronic relapsing-remitting condition that causes chronic inflammation of the gastrointestinal tract. The clinical presentation of CD is often characterised by malnutrition, abdominal pain, diarrhoea, and weight loss.[33] Despite the availability of a variety of therapeutic options used in the management of CD (medications, surgical, or nutritional), none of these options lead to complete cure of this condition. [32] The main objective of any given management option is to induce and then maintain remission of disease activity by controlling the extent of inflammation, reducing clinical symptoms, and preventing complications. Although corticosteroids are the most widely used drugs for the treatment of active CD, their use has been shown to be associated with short-term remission, steroid dependency, impairment in growth, and risk of infections.[33]

For the past two decades, nutritional therapy/enteral nutrition has been suggested as an effective treatment option in the management of CD in adults and children in terms of controlling CD activity.[31, 37] For example, one meta-analysis indicated that enteral nutrition was at least as effective as steroids in inducing remission in children and young adults with active CD.[36] In contrast, a more recent review demonstrated that enteral nutrition given to adults was in general beneficial but less effective in inducing remission compared to steroids.[27] There has been little clarity as regards to the role of enteral nutrition for maintaining remission in patients with quiescent CD. The relevant evidence has been scarce, mostly of observational nature, and inconsistent in terms of findings.[33, 37] Owing to its good safety profile, and if proved at least as effective as standard medical treatments, enteral nutrition would potentially replace or minimise the use of steroids, biologics, immunosuppressants. This in turn would lead to improved clinical outcomes, fewer adverse events, in general, and better growth rates and pubertal development in younger patients with CD.[35, 37]

The mechanism of action of elemental nutrition on CD is not known. Several hypothesised mechanisms underlying the proposed benefits of enteral nutrition in CD include reduced gut activity, reduction of antigenic load, nutritional effects, anti-inflammatory effects, or modulation of immune system and gastrointestinal flora.[30-33]

5.1 Main findings

This review systematically identified, appraised, and synthesised relevant evidence on the comparative clinical effectiveness of elemental nutrition for maintaining remission in patients with CD. Limited

evidence from two RCTs[50, 52] and three non-RCTs[30, 56, 57] has suggested that elemental nutrition (given orally or via feeding tube) was more effective for the maintenance of remission (at 12-48 months; very low grade evidence based on RCTs) and prevention of relapse (at 12-24 months; high grade evidence based on RCTs) compared to no treatment (i.e., unrestricted diet). Evidence from one non-RCT also indicated that patients receiving elemental nutrition experienced longer mean time to relapse compared to patients in the no intervention group on unrestricted diet only.[56] The 12-month rates of adherence were lower in the elemental nutrition vs. no intervention (i.e., unrestricted diet)[30, 56] or polymeric nutrition group.[55] This finding may be explained by the inconvenience of nasogastric feeding, poor palatability, and/or higher cost of elemental nutrition compared to unrestricted diet and polymeric nutrition.[31, 61] Limited evidence from one RCT[52] demonstrated no difference in health related quality of life between elemental nutrition and no intervention (unrestricted diet).

In general, comparisons of elemental nutrition to active treatments (sulfasalazine/prednisolone, infliximab, elemental nutrition, polymeric nutrition, or combination) across the outcomes of interest were not statistically significant. These results should not be interpreted to mean that the treatments being compared are equivalent (or that there is an absence of effect of elemental nutrition). The associated 95% CIs tended to be so wide and uninformative as to include potential moderate to large treatment effects compatible with both benefit and harm of elemental nutrition. Therefore, these results are inconclusive.

The data on complications and adverse events was too sparse (e.g., zero events, low counts) to derive effect estimates and 95% CIs or to permit any meaningful comparison between the treatments. It is unclear whether insufficient evidence on adverse events and complications is due to the absence or rarity of these events or it is simply due to underreporting of such events.

For some reported evidence (e.g., cumulative probability of survival for being in remission) adequate interpretation was not possible due to poor reporting or missing data (no summary effect measures, 95% CIs, standard deviations), and therefore was considered inconclusive.

5.2 Limitations of evidence

The review findings warrant cautious interpretation given the limitations of the evidence in terms of small trial size, methodological quality, and risk of bias in individual trials (lack of blinding, short duration of follow-up, confounding).

For example, the lack of blinding of participants, study personnel, and/or outcome assessors may have led to systematic differences in care giving, administration of co-interventions, and outcome assessments across the compared treatment groups. Generally, subjective measures such as those based on patient-reported outcomes including clinical symptoms (e.g., abdominal pain, number of soft stools), quality of life, or clinically defined remission/relapse) are more prone to bias than objective outcomes (e.g., endoscopic or biologically defined remission using serum/faecal biomarkers and radiography additional to CDAI, adverse events, and complications).

Some of the results, especially in non-RCTs, may have been biased since some known or unknown prognostic factors may have been distributed unevenly between the treatment groups. As for the known confounders, there was some between-group imbalance in two non-RCTs with regards to induction therapy, location of the lesion, and disease duration.[51, 56] Moreover, in three non-RCTs[30, 57, 58] patients with 'good compliance' were assigned to elemental nutrition and those with 'poor compliance' to the control groups. Given that 'good compliers' may be inherently different from 'poor compliers' in clinical characteristics, this selective assignment could have distorted the group balance in some of these prognostic covariates (unclear risk of bias). Additional concern for confounding effects is justified since in some of the studies the use of concomitant drugs given for prophylaxis (e.g., 5-ASA, sulphasalazine, azathioprine, prednisolone) differed across the treatment groups in frequency/dose.[30, 50, 52, 55, 56, 58]

In general, more or less consistent results for primary outcomes observed between RCTs and non-RCTs give more credence to the validity of findings in this review.

Additional limitations of the relevant evidence are worth mentioning. There was a lack of evidence of effects of elemental nutrition in young adolescents and children with CD in remission. The data reported on health related quality of life, adverse events, and complications were insufficient to allow any adequate conclusion. There was no relevant evidence for changes in anthropometric measures (weight, BMI, height, linear growth) and pubertal development. Given that all of the included studies evaluated elemental nutrition in addition to restricted or unrestricted diet, this review was unable to assess the effectiveness of an exclusive elemental nutrition in the maintenance of remission in patients with CD.

5.3 Comparison of current findings to previous systematic reviews

We identified two SRs evaluating comparative effectiveness of elemental nutrition in maintaining remission for patients with CD.[32, 37] The Cochrane review's eligibility criterion for design was set to

RCTs (included two RCTs).[32] The study eligibility for the other SR was wider and encompassed RCTs, prospective non-randomised controlled trials, and retrospective observational cohort studies (included one RCT, three non-RCTs, and six retrospective cohort studies).[37] All potentially eligible trials included in the two SRs, were also included in the present review. In general, findings of this review are in agreement with those from other two SRs in showing benefits of elemental nutrition compared to no intervention (i.e., unrestricted diet) in maintaining remission amongst patients with CD. In agreement with our review, findings in relation to the comparison between elemental and polymeric nutrition were inconclusive.[32]

5.4 Strengths and limitations of current review

One of the strengths of this review is that we used systematic, comprehensive, and independent strategies to minimise bias in searching, identifying, selecting, extracting, and appraising the primary studies. The search strategy was applied to multiple electronic sources, relevant websites, as well as reference lists of potentially eligible publications were searched. Moreover, this review included a higher hierarchy of evidence (i.e., randomised and non-randomised controlled trials).

This review has its own limitations. The presence of clinical heterogeneity (e.g., population characteristics, induction therapy), potential for confounding (especially in non-RCTs), and poor reporting (missing data on outcomes) led to limitations for pooling the results across studies. Since this review included only English language full text publications, the effects of publication bias cannot be ruled out. Given the insufficient number of pooled studies (data points), this effect could not be investigated via funnel plots. Likewise, the paucity of data did not allow exploration of whether there was any variation in treatment effect across the pre-defined subgroups of patients or methodological features of studies.

5.5 Applicability of findings and implications for clinical practice and policy making

It is not usually easy to determine the extent to which studies are applicable to a broader context of routine clinical practice in a given geographical place and this is true in this case for extrapolating to the UK for a number of reasons. This process of ascertaining applicability is hindered by poor reporting, selective eligibility criteria and enrolment, non-participation and differences between treatments and outcomes used in research versus those used in routine clinical practice. Specifically, the extent of

applicability of this review's findings to clinical practice in the UK may be limited, since six of the eight included studies were conducted in Japan,[30, 50-52, 57, 58] and only two in the UK.[55, 56] The trials reviewed may have been overly selective in enrolling and assigning patients to treatments, thereby leading to samples that are not representative of patients with CD in remission encountered in daily clinical practice. Patient adherence is important for successful treatment with elemental nutrition. However, if studies have reported the effects of elemental nutrition in only good compliers, this will also limit the applicability of findings to a broader group of patients. Since all included studies investigated adult patients, the conclusions regarding the benefits of elemental nutrition in maintaining remission of CD may not be readily applicable to younger patients (< 18 years old). Most results were based on outcomes ascertained at 12-24 months of follow-up. The conclusions of the review regarding longer-term benefits indeterminate and cannot be extrapolated. Finally, our findings may not be readily applicable to patients receiving exclusive elemental nutrition, since the evidence available to us and which we reviewed presented only those scenarios where elemental nutrition was given in addition to diet. In summary we would counsel caution in attempting to extrapolate the findings of this review to practice in the UK and would recommend that further research is required – please see research recommendations.

5.6 Implications for future research

Large well-powered and long-term randomised trials are needed to either refute or corroborate our findings. Future research needs to address gaps in the reviewed evidence (e.g., studies in young adolescents and children with CD in remission; effects of exclusive elemental nutrition; effects of elemental nutrition in subgroups defined by age, sex, duration/location of CD, and type of induction therapy) and improve reporting practices in relation to trial methodology (e.g., methods of treatment assignment, blinding, power analysis, statistical analysis) as well as completeness of reported data (missing effect estimates, 95% CIs, adverse events, complications) for better interpretability of evidence. More research exploring better tasting elemental nutritional to maximise the adherence rate to elemental nutrition feeding is also warranted.

6 CONCLUSIONS

This systematic review assessed comparative clinical effectiveness of elemental nutrition for the maintenance of remission in patients with CD based on evidence from eight prospective controlled studies. Overall, the findings warrant cautious interpretation given the limited amount of evidence (small number of studies), methodological shortcomings (short-term follow-up, small studies), poor reporting (missing data, partial reporting of data), and role of bias which cannot be ruled out (adherence to elemental nutrition, confounding, lack of blinding). Given these caveats, the results from five studies indicated significant benefits of elemental nutrition (given orally or via feeding tube) in maintaining remission and preventing relapse compared to no intervention (i.e., unrestricted diet) at 12 to 48 months of follow-up. A limited amount of evidence showed greater patient adherence rates for unrestricted or polymeric nutrition groups compared to an elemental nutrition group at 12 months follow-up. According to evidence from one trial, there was no difference in health related quality of life between patients receiving an elemental vs. an unrestricted diet after 12 months of follow-up. In general, effect estimates for most outcomes across comparisons between elemental nutrition and active treatments (e.g., prednisolone) were statistically non-significant accompanied by a great degree of uncertainty (very wide 95% CIs) and therefore were rendered inconclusive. There was a lack or insufficient evidence on adverse events and complications and no evidence on cost effectiveness. There was no similar evidence reported for children or younger patients with CD in remission. Future large and long-term randomised trials are warranted to draw more definitive conclusions regarding the effects of elemental nutrition in maintaining remission in CD.

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8 APPENDICES

8.1 Appendix I: Protocol

1. Title of the project

Elemental nutrition for Crohn's disease

2. Name of TAR team and project 'lead'

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3. Plain English Summary

Crohn's disease (CD) is a chronic relapsing-remitting condition that causes inflammation of the intestines. Frequent symptoms of CD include malnutrition, abdominal pain, and diarrhoea. None of the currently available therapeutic options (e.g., medical, surgical, nutritional) lead to a complete cure of CD. The management involves induction and maintenance of remission of disease activity through alleviating inflammatory process and correcting malnutrition. In children, a major additional goal is to promote normal growth and pubertal development. Although there is some evidence indicating beneficial effects of elemental diet for induction of remission in patients with active CD, clinical evidence regarding the role of elemental diet in maintaining remission in CD has not been well studied or clarified. This systematic review aims to evaluate recent comparative evidence on clinical effectiveness and cost-effectiveness of elemental diet for the maintenance of remission in patients with CD.

4. Decision problem

Objectives

The general objective of this systematic review is to identify, appraise, and evaluate the evidence on clinical effectiveness and cost-effectiveness of elemental diet, a type of enteral nutrition (EN), for the maintenance of remission in Crohn's disease (CD).

- To evaluate the clinical effectiveness and cost-effectiveness of elemental nutrition administered alone or in combination with other interventions (e.g., diet, standard drug treatment) compared to other intervention(s) (e.g., placebo, diet, standard drug treatment) for maintaining remission in patients with CD.
- To compare the clinical effectiveness and cost-effectiveness of elemental nutrition with other types of EN (semi-elemental, polymeric nutrition), duration, and dose in regards to maintaining remission and adherence.
- To explore subgroup effects of elemental nutrition on maintenance of remission (i.e., risk of relapse or recurrence). Specifically, to examine if the treatment effect of elemental nutrition varies across groups defined by sex (males, females), age (adults, adolescents, and children), and type of induction therapy (medically-, nutritionally-, surgically-induced).
- To evaluate additional outcomes for patients with CD such as adherence to EN, CD activity index (CDAI), incidence of mucosal healing, quality of life, adverse events, gain in body weight (or body mass index), growth, and pubertal development.

4.1 Background

Crohn's disease (CD), a form of inflammatory bowel disease (IBD), is a chronic relapsing-remitting condition which causes chronic inflammation of the intestines. CD can affect any part of the digestive tract, from the mouth to the anus.[1] The most frequent symptoms of CD include malnutrition, abdominal pain, diarrhoea, weight loss, fever, and rectal bleeding. Although currently there are medical (e.g., corticosteroids, biologics, aminosalicylates, immunosuppressants, tumor necrosis factor inhibitors, antibiotics), endoscopic/surgical (indicated for complications such as bowel obstruction, high grade dysplasia, abscess, internal fistulas, and cancer), and nutritional (e.g., enteral feeding, restricted diet, parenteral feeding) therapeutic options available to patients with CD, none of them leads to complete cure of this condition.[1,2] Therefore, the management of the disease usually involves the induction and maintenance of remission of disease activity by controlling the extent of inflammatory process, correcting malnutrition, as well as reducing symptom presentation and occurrence of complications.[2,3] In children, a major additional goal is to facilitate normal growth and pubertal development which are frequently impeded.

The choice of therapeutic options depends largely on the extent of inflammation, the disease severity, and complications. Any therapeutic recommendation needs to consider a balance between individual response in terms of beneficial effects, treatment-related adverse events, and long term complications.[2,3] Corticosteroids are most widely used agents for the management of active CD. However, their use is associated with high risk of relapse, low rates of mucosal healing, steroid dependency, and other adverse events (e.g., growth impairment, infections). There have been safety concerns with long term use of other agents such as tumor necrosis factor (TNF) inhibitors.[1]

Nutritional therapy has played an important but controversial role in the alleviation of malnutrition and control of disease activity in patients with active CD. There is some evidence on clinical benefits and long term safety of EN in inducing remission in patients, especially children and young adults with active CD.[4,5] For example, in Japan, EN is recommended as the first-line treatment in the management of active CD.[1,6] Although EN has been shown to be an effective and safe intervention for induction of remission in patients with active CD, withdrawal of EN and resumption of normal diet would often be followed by reoccurrence of gastrointestinal symptoms and use of corticosteroids.[7] Evidence comparing clinical effectiveness of EN to corticosteroids for the induction of remission has been inconsistent, with one meta-analysis showing no difference between the two,[5] and more recent meta-analysis indicating a superiority of corticosteroids over EN.[8]

Equally important evidence on the efficacy of different types of EN (i.e., elemental, semi-elemental, polymeric) in maintaining remission in CD has been insufficient and less clear.[1,6,7,9] If EN proves to be at least as effective as conventional medications, its use might minimize or replace the use of steroids, biologics, and immunosuppresants.[1,6,7]

Most evidence on the comparative clinical effectiveness of EN in the maintenance of CD remission rests upon retrospective observational cohort studies and prospective non-randomised controlled experimental trials.[1,6,9] The similar evidence from RCTs is insufficient due to difficulties with consent and adherence of patients assigned to EN.[7,10-12] In general, retrospective observational cohort studies pose difficulties in establishing causality due to their methodological limitations.[6] For example, given the retrospective nature of such studies, temporality between the occurrence of exposure and outcome is unclear or indeterminate. Furthermore, since retrospective studies utilize the patient data that had been collected for other purposes than the question of interest, these studies may not be able to adjust the effect estimates of elemental nutrition for many important confounders (e.g., disease activity, smoking, age, adherence, co-morbidities, nutritional status) since such data had not been collected.

In order to bring more clarity to this area, this review aimed to evaluate evidence on clinical effectiveness and cost-effectiveness of elemental diet (a type of enteral nutrition) for the maintenance of remission in CD. Given the above-mentioned limitations of retrospective observational cohort studies in establishing causality, this review will focus on higher hierarchy of evidence by including only prospective studies, i.e., randomised and non-randomised controlled clinical trials.

4.2 Report methods for synthesis of evidence

Search strategy

Scoping searches have been undertaken to inform the development of the search strategy and assess the volume and type of literature relating to the assessment question. We used an iterative procedure with input from clinical advisors and previous systematic reviews.[6,7,13] The yield of 324 records from the search developed for MEDLINE, before any limits were applied or any sifting was undertaken, demonstrated that there is limited evidence in this area (see Appendix 1).

A copy of the main database search strategy that is likely to be used in the major databases is provided in the Appendix 1. This draft search strategy, developed for MEDLINE, will be adapted as appropriate for other databases and will include the concepts of CD, remission and elemental nutrition. This strategy will not include limits for study design, language or publication date, as the number of articles to sift identified in the scoping search is not anticipated to be high.

The overall search strategy will comprise the following main elements:

- Searching of electronic bibliographic databases and trial registries
- Supplementary searching (including scrutiny of references of included studies, citation searching, searching relevant websites)
- Contact with clinical advisors in the field

Databases will include:

MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE (via OVID); CDSR, CENTRAL, DARE, NHS EED, HTA database (via the Cochrane Library); Science Citation Index and Conference Proceedings (via Web of Knowledge); WHO ICTRP; UKCRN Study Portfolio.

Citation searches of included studies will be undertaken using the Web of Science citation search facility. The reference lists of included studies and relevant review articles will also be checked. Clinical advisors in the field will be consulted and websites of relevant organisations checked.

Two supplementary database searches using limits will be undertaken. The first, combining CD with the concept of nutrition therapy and limited to systematic reviews or cost-effectiveness, will aim to capture any articles that include the assessment question as part of a broader systematic review or cost study. The second, combining CD with the concept of elemental nutrition and limited to relevant study types, will aim to capture any articles that include our population as part of a controlled clinical trial of both active CD and CD in remission.

All retrieved records will be collected in a specialised database. All duplicate records will be identified and removed.

Study eligibility criteria

*Inclusion criteria**:***

Type/language of publication

English full text and abstracts (only if companion publications to full text included studies)

Study design

RCTs and prospective non-randomised controlled clinical trials

Population

Adults, young people, or children with CD in remission (inactive, quiescent CD) at the time of study baseline

Intervention

- Elemental nutrition via oral passage, nasal passage (naso-gastric tube, naso-jejunal tube, naso-duodenal tube), or direct passage via the abdomen (gastrostomy tube, jejunostomy tube) alone
- Elemental nutrition in combination with other intervention(s) (e.g., standard drug therapy, restricted diet)

Comparator

- Enteral nutrition (elemental, semi-elemental or polymeric nutrition) alone, normal unrestricted diet alone (i.e., no intervention), restricted diet alone, standard drug therapy alone, any other intervention or placebo.
- Enteral nutrition (elemental, semi-elemental or polymeric nutrition) in combination with other intervention(s) (e.g., standard drug therapy, restricted diet, any other intervention or placebo)

- Any combination of standard drug therapy, restricted diet, any other intervention, and/or placebo

*Exclusion criteria**:***

a) Induction studies (patients with active CD at baseline) with or without follow up of remitted patients receiving maintenance therapy
b) Studies of parenteral (intravenous) nutrition
c) Studies of ulcerative colitis
d) Reviews, meta-analyses, case-reports, case-series, retrospective observational studies, editorials, comments
e) Studies employing non-concurrent (e.g., historical) controls
f) Studies with mixed patient population (< 80% Crohn's disease)
g) Studies comparing different nutrition/diets of elemental nutrition

<u>Outcomes – clinical effectiveness</u>

Adult populations

a) Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], duration of remission) – primary outcome
b) Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) – primary outcome
c) Incidence of mucosal healing – primary outcome
d) Need for surgery (n/N)
e) Withdrawal from steroids (n/N)
f) Steroid dose tapering (n/N)
g) CDAI (measured as continuous or categorical outcome)
h) Quality of life (QOL)
i) Adverse events (treatment-related)
j) Complications of CD
k) Gain in body weight or body mass index
l) Adherence

Younger populations (e.g., adolescents, paediatric)

a) Maintenance of remission (% patients in remission at end of follow-up, cumulative probability of maintaining remission [Kaplan Meier estimate of survival], duration of remission) – primary outcome
b) Development of relapse/recurrence (proportion of patients developing relapse/recurrence [n/N], time to relapse/recurrence [mean # of months]) – primary outcome
c) Incidence of mucosal healing – primary outcome
d) Need for surgery (n/N)
e) Withdrawal from steroids (n/N)
f) Steroid dose tapering (n/N)
g) CDAI (measured as continuous or categorical outcome)
h) Quality of life (QOL)
i) Adverse events (treatment-related)
j) Complications of CD
k) Gain in body weight or body mass index
l) Adherence
m) Growth
n) Pubertal development

Outcomes – cost-effectiveness

a) Costs (no efficacy measures: cost-minimization analysis)
b) Costs and efficacy measures - clinical and quality-adjusted life years (full economic analysis)
c) Incremental cost-effectiveness ratios (full economic analysis)
d) Results from cost-effectiveness acceptability curves

Study selection strategy

Two independent reviewers will screen all identified bibliographic records for title/abstract and then for full text using a pre-specified and piloted questionnaire form. The study flow and reasons for exclusion of full text papers will be documented in the PRISMA study flow diagram (Appendix 2).[14]

Data extraction strategy

Two reviewers will independently extract relevant data using an *a priori* defined pre-piloted extraction sheet (Appendix 3). The extracted data will be cross-checked and any disagreements will be resolved by discussion or by recourse to a third party reviewer. The extracted data will include study (e.g., author, country, design, sample size, follow-up duration, risk of bias items), participant (e.g., age, sex, inclusion/exclusion criteria, CD activity index, clinical/endoscopy definitions of CD remission, type of induction therapy), intervention/comparator (brand name/manufacturer of EN; type, mode, duration, and dose of administration of EN, any concomitant diet or dietary restriction, and other co-intervention such as medications), and outcome characteristics (e.g., scale of measurement, timing of assessment, definition of CD relapse/recurrence).

For individual studies, the dichotomous and continuous summary clinical effectiveness outcome measures of association will be summarized as risk/odds ratio, mean difference, and measures of variability (p-value, 95% confidence interval). If needed and data allows, we will attempt to calculate missing statistical parameters (e.g., risk ratios, mean differences, standard deviations, standard errors, and 95% confidence intervals) for primary clinical outcomes of interest (e.g., risk of relapse, time to relapse, quality of life, weight gain, CD activity index). All calculated parameters will be entered into the data extraction sheets and will be marked as 'calculated'.

Individual study quality assessment strategy

Two reviewers will independently assess the methodological and reporting quality of included individual studies. Any disagreements between the two reviewers will be resolved by a third reviewer through a discussion.

RCTs will be assessed using the Cochrane Collaboration Risk of Bias (ROB) tool[15] which covers the following domains of threat to internal validity: selection bias (randomisation sequence generation, treatment allocation concealment), performance bias (blinding of participants/personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data – primary outcome), reporting bias (selective outcome/analysis reporting), and other pre-specified bias (e.g., funding source, adequacy

of statistical methods used, type of analysis, baseline between-group imbalance in important prognostic factors). The risk of bias assessment falls into three categories of high, low, and unclear risk of bias. The assessments will be provided in ROB tables and summary graph (Appendix 4). Prospective non-randomised controlled clinical trials (CCTs) will be assessed using a modified Cochrane ROB tool in which the domain of selection bias will be evaluated in regards to baseline between-group imbalance for important prognostic factors instead of randomisation sequence generation and treatment allocation concealment (Appendix 5). For each study (RCT or non-RCT), the risk of performance, detection, and attrition bias domains for subjective (e.g., patient-administered clinical or quality of life scores) and objective (e.g., presence of remission, relapse/recurrence, time to relapse, weight gain, mucosal healing, growth, adverse events) outcomes will be assessed separately. Afterwards, within-study summary ROB rating across all domains will be derived for subjective and objective outcome groups separately (Appendix 6). At data synthesis stage, across-study average summary ROB will be determined and assigned to each outcome of interest.

The quality of economic analyses of the included studies will be assessed using the Drummond 10-item checklist (Appendix 7).[16]

Data analysis and synthesis

Study, treatment, population, and outcome characteristics will be summarised in text, evidence, and summary tables. The study results on the relative effectiveness of EN for each outcome of interest and cost-effectiveness will be compared qualitatively and quantitatively in text and summary tables.

In the clinical effectiveness part of the review, results for any given outcome measures will be presented separately stratified by a) induction therapy (medically-, nutritionally-, surgically-induced remission), b) age (adult vs. paediatric), and c) regimen (elemental, semi-elemental, polymeric nutrition, dose, mode of administration).

The decision to pool individual study results will be based on a degree of similarity with respect to methodological and clinical characteristics of studies under consideration (e.g., design, population, comparator treatment, and outcome). Estimates of post-treatment mean difference for continuous outcomes and RRs for binary outcomes (except for rare events) of individual studies will be pooled using a DerSimonian and Laird random-effects model.[17] Dichotomous outcomes with low event rates (5.0%-10.0%) will be pooled as RR using a Mantel-Haenszel fixed-effects model. Dichotomous outcomes for studies with very low event rates ($\leq$ 5.0%) or zero events in one of the treatment arms were pooled as

odds ratio (OR) using a Peto fixed-effects model.[18] Trials will not be pooled if the mean and/or standard deviation for the continuous outcome of interest cannot not be ascertained.

The degree of statistical heterogeneity across pooled studies will be determined through inspection of the forest plots, Cochran's Q and the I^2 statistics. The heterogeneity will be judged according to pre-determined levels of statistical significance (Chi-square $p < 0.10$ and/or $I^2 > 50\%$). If data allows, study-level clinical and methodological sources of heterogeneity of effect estimates across studies will be explored through *a priori* defined subgroup analysis (i.e., age, sex, induction therapy) and sensitivity analysis (risk of bias item-specific ratings, intention-to-treat vs. per protocol analysis).

Given a sufficient number of data points, publication bias will be assessed through visual inspection of funnel plots with respect to plot asymmetry and use of linear regression tests.[19]

Overall quality of evidence (GRADE system)

The overall quality of evidence for pre-selected gradable outcome (risk of CD relapse/recurrence) across studies will be assessed using the systematic approach developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org).

The GRADE approach[20] indicates level of confidence in the observed treatment effect estimate(s) and is based on assessments across five domains: a) summary ROB across studies per gradable outcome (internal validity across studies; study limitations), b) consistency of results (heterogeneity), c) directness of the evidence (applicability of the results), d) precision of the results (the width of 95% CI around the estimate), and e) publication/reporting bias (detection of asymmetry in the funnel plot; selective outcome reporting). The overall quality of evidence is categorized as high, moderate, low, or very low grade. Initial grade of RCTs will be rated as high and will be downgraded by one point (e.g., from high to moderate) if any of the five criteria is not met. Initial grade for non-RCTs will be rated as low and will be upgraded by one point (e.g., from low to moderate) if any of the three criteria for upgrading a grade is met (e.g., dose-response gradient, large magnitude of effect, and adjustment for confounders).[21] The process of assessment of overall quality of evidence grading will be provided in Appendix 8.

4.3 Results section

The review results will be organised in text and tables (evidence and summary tables). The summary tables will tabulate characteristics, methodological quality, and results for included primary studies.

Tables for primary studies will present summary data on participants (age, gender, number/range of participants), interventions (enteral diet, comparator), outcomes (e.g., type, summary effect measures, 95% CIs, timing), and settings (e.g., primary care, specialty clinic). Meta-analyses of primary studies will be presented in forest plots accompanied by measures of heterogeneity. If pooling is not feasible, due to the lack of sufficient data or important clinical/statistical heterogeneity across studies, the findings from individual studies will be summarised narratively. Evidence for each outcome of remission maintenance from one or more studies (either un-pooled or pooled) will be summarised and graded accordingly, and presented in a tabular form.

4.4 Discussion section

This section will cover the interpretation and validity of the findings of the review in light of available evidence and the review methodology. We will highlight and discuss strengths and limitations of the review and their likely influence on the effect estimates. The stability of treatment effect measures will be explored and discussed. Future research implications of the review findings will also be discussed. Identified gaps/inconsistencies in the current knowledge (e.g., heterogeneity, lack or insufficiency of evidence) and methodological limitations of the reviewed evidence (e.g., study design, risk of bias in primary studies, short term follow-up, inadequate sample size, outcome measurement methods) will be highlighted and corresponding recommendations for future research directed at mitigation of these limitations will be outlined. Where possible, the recommendations will be of sufficient detail and clarity to form the basis of a future commissioning brief (e.g., PICO and suggested study type).

Unlike most of the previously published reviews, this review will employ a systematic approach by focusing only on higher level hierarchy of evidence (randomised and non-randomised controlled clinical trials) with the purpose of elucidating the role of enteral diet in the maintenance of CD compared to other treatments. Moreover, it will provide an updated evidence base on this topic and will be better equipped in determining comparative clinical and cost-effectiveness of enteral diet for the maintenance of remission in CD.

We anticipate that this review will better inform researchers, clinicians, and policy makers in deriving more robust recommendations for appropriate treatment choices in the maintenance of CD, and serve as an impetus towards improved conduct, methodology, and reporting of future studies in this area.

5. Expertise in this TAR team

Warwick Evidence is a technology assessment group located within Warwick Medical School. Warwick Evidence brings together experts in clinical and cost effectiveness reviewing, medical statistics, health economics and modelling. The team planned for the work includes: Dr Paul Sutcliffe, Dr Alexander Tsertsvadze and Dr Tara Gurung, who are experienced systematic reviewers; Mrs Rachel Court, information specialist; Ruth Pulikottil-Jacob, provides modelling and health economic expertise; Professor Aileen Clarke, Dr Ngianga-Bakwin Kandala provide epidemiological and statistical expertise; Dr Ramesh Arasaradnam, University Hospital, Coventry, and Professor Simon Murch, University of Warwick, will provide clinical advice.

6. Competing interests of authors and advisors

None of the authors have any competing interests.

7. Timetable/milestones

Draft protocol finalised	TBC
Commissioning decision	TBC
Anticipated start date	1 October 2013
Progress report	15 November 2013
Final assessment report	11 January 2014

8. Team members' contributions

Research team:	Warwick Evidence
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9. Clinical Advisors

1) Dr Ramesh Arasaradnam: Gastroenterology, University Hospital, Coventry. His clinical and research interests are in gut physiology, nutrition, inflammatory and cancer biology.

2) Professor Simon Murch: Professor of Paediatrics, Warwick Medical School, Coventry. His research background is in mucosal immunology, and his early work was based on the role of macrophage cytokines in intestinal and lung inflammation. This work contributed to the introduction of anti-TNF therapy in Crohn's disease, and also provided the first demonstration of the role of inflammatory cytokines in lung disease affecting preterm infants.

Contribution of above clinical advisors include: protocol development, help interpret data, provide a methodological, policy and clinical perspective on data and review development of background information and clinical effectiveness and review of report drafts.

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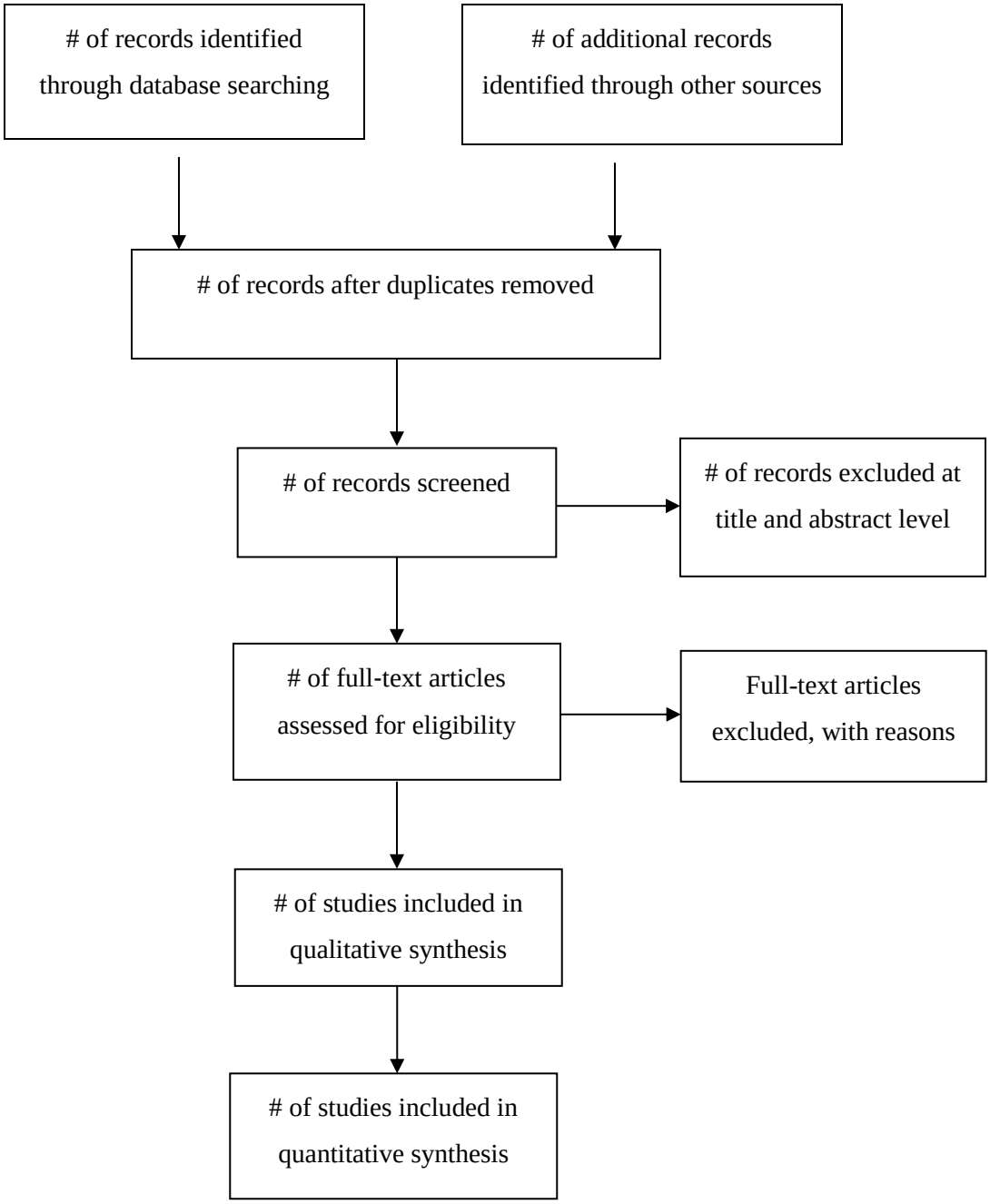
Appendices

Appendix 1. Draft search strategy details

Ovid MEDLINE(R) 1946 to May Week 5 2013, searched on 13 June 2013

1	Crohn Disease/	29507
2	Inflammatory Bowel Diseases/	12777
3	crohn*.tw.	29987
4	Inflammatory bowel disease*.tw.	23863
5	IBD.tw.	10207
6	1 or 2 or 3 or 4 or 5	53451
7	remission*.tw.	83291
8	inactiv*.tw.	227468
9	quiescen*.tw.	20271
10	disease-free survival/	41204
11	relaps*.tw.	111733
12	recurr*.tw.	348455
13	maintenance.tw.	175893
14	7 or 8 or 9 or 10 or 11 or 12 or 13	923305
15	6 and 14	8307
16	((enteral or elemental or chemically defined) and (nutrition* or diet* or feed*)).tw.	13181
17	Enteral Nutrition/	15194
18	Food, Formulated/	5229
19	16 or 17 or 18	24823
20	15 and 19	324

Appendix 2. PRISMA study flow diagram



Appendix 3. Data extraction sheet for included primary study reports

Name of first reviewer:
Name of second reviewer:

Study details				
First author surname year of publication: **Country**: **Study design**: **Study setting** (primary care/specialty clinic/other - specify): **Number of centres**: **Total length of follow up**: **Funding** (government/private/manufacturer/other - specify):				
Aim of the study				
Participants				
Recruitment dates: **Total N of patients who received induction therapy**: **Total N of patients achieving remission after induction therapy**: **Total N of patients failing to achieve remission after induction therapy:** **Total N of patients excluded before start of maintenance therapy (e.g., lost to follow up):** **Total number of patients allocated to maintenance treatment**: **Inclusion criteria**: **Exclusion criteria**: **Characteristics of participants (total study sample)** Mean (range or SD) age (years): Women (n [%]): Race/ethnicity (n [%]): Diagnostic criteria for CD: Mean Crohn's Disease Activity Index (CDAI) (range or SD): CD location: Type of induction therapy (n [%]):				
Intervention				
Elemental diet group: **Intervention 2 group**: **Intervention 3 group**:				
Outcomes (study-based)				
Primary outcomes (*list*): **Measure of disease activity (clinical, endoscopic):** **Definition of remission (clinical, endoscopic):** **Definition of relapse/recurrence (clinical, endoscopic):** **Definition of mucosal healing (clinical, endoscopic):** **Post-baseline timings of primary outcome assessment:**				
Number of patients				
	Total	**Elemental diet group**	**Intervention 2 group**	**Intervention 3 group**
Allocated to treatment				
Analysed (If more than one follow-up, choose and specify the last				

one)				
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)				

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental diet group		
Intervention 2 group		
Intervention 3 group		

Patient baseline characteristics			
	Elemental diet group	**Intervention 2 group**	**Intervention 3 group**
Age (years) Mean (SD)			
Sex –female n/N (%)			
Weight (kg) Mean (SD)			
BMI (kg/m^2) Mean (SD)			
Smoking n/N (%)			
Previous bowel resection n/N (%)			
Duration of CD (months) Mean (SD)			
Crohn's Disease Activity Index (CDAI) Mean (SD)			
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)			
Disease activity other than CDAI (specify)			
Mucosal ulceration n/N (%)			
Other complications n/N (%)			

Efficacy outcomes				
For each timing of assessment please provide a separate table *For scores, extract only total scores* Post-procedural follow-up assessment timing (Specify):				
	Elemental diet group	**Intervention 2 group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)				
Duration of remission (months) Mean (SD) or 95% CI				
Risk of relapse or recurrence n/N (%)				
Time to relapse (months) Mean (SD) or 95% CI				
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)				
Patients achieving mucosal healing n/N (%)				
Crohn's Disease Activity Index (CDAI) Mean (SD)				
The Short Form Health Survey (SF-36) Mean (SD) 95% CI				
The Short Form Health Survey (SF-12) Mean (SD) 95% CI				
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI				

Other HQOL (specify) Mean (SD) 95% CI				
Weight (kg) Mean (SD) 95% CI				
Weight gain (kg) Mean change (SD) 95% CI				
Body mass index (kg/m^2) Mean change (SD) 95% CI				
Height gain (cm) Mean (SD) 95% CI				
Linear growth rate (mean height-for-age Z-score)				
Adherence n/N (%)				
Need for surgery n/N (%)				
Steroid dose tapering n/N (%)				
Withdrawal from steroids n/N (%)				
Adverse events due to treatment n/N (%)				
Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]				
	Elemental diet group	**Intervention 2 group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)				
Delay in pubertal development n/N (%)				
Bowel obstruction				
Fistulae				
Abscess				
Colon/bowel cancer				
Intestinal infection				
Others (Specify)				
Authors conclusion				
Reviewer's conclusion				

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Appendix 4. The risk of bias assessment of included randomised controlled trials (adapted from Higgins et al. 2011)[15]

Name of first reviewer:
Name of second reviewer:
First author surname year of publication:

Bias domain	**Source of bias**		**Support for judgment***	**Authors' judgment****
Selection bias	Random sequence generation			
	Allocation concealment			
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)		
		Objective (e.g., radiography, endoscopy)		
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)		
		Objective (e.g., radiography, endoscopy)		
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)		
		Objective outcomes (e.g., radiography, endoscopy)		
Reporting bias	Selective reporting of the outcome, subgroups, or analysis			
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP], baseline imbalance in important characteristics			
ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias				

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Appendix 5. The risk of bias assessment of included non-randomised controlled trials (adapted from Higgins et al. 2011)[15]

Name of first reviewer:
Name of second reviewer:
First author surname year of publication:

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)			
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)		
		Objective (e.g., radiography, endoscopy)		
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)		
		Objective (e.g., radiography, endoscopy)		
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)		
		Objective outcomes (e.g., radiography, endoscopy)		
Reporting bias	Selective reporting of the outcome, subgroups, or analysis			
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]			
ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias				

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Appendix 6. Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias	

Appendix 7. Methodological quality of economic evaluations in included studies (The Drummond Checklist[16])

Item#*	Study #1	Study #2	Study #3	Study #4	Study #5	Study #6	Study #7	Proportion of studies with 'Yes' (%)
Item 1								
Item 2								
Item 3								
Item 4								
Item 5								
Item 6								
Item 7								
Item 8								
Item 9								
Item 10								

*Responses to items: Yes, No, Can't Tell

Item 1: Was a well-defined question posed in answerable form?
Item 2: Was a comprehensive description of the competing alternatives given?
Item 3: Was the effectiveness of the programmes or services established?
Item 4: Were all the important and relevant costs and consequences for each alternative identified?
Item 5: Were costs and consequences measured accurately in appropriate physical units (e.g. number of physician visits, lost work-days, gained life-years)?
Item 6: Were costs and consequences valued credibly?
Item 7: Were costs and consequences adjusted for differential timing?
Item 8: Was an incremental analysis of costs and consequences of alternatives performed?
Item 9: Was allowance made for uncertainty in the estimates of costs and consequences?
Item 10: Did the presentation and discussion of study results include all issues of concern to users?

Appendix 8. GRADE evidence profile for gradable outcomes (adapted from Guyatt et al., 2011[20])

Outcome [follow-up timing]	N of studies reporting outcome (participants)	Pooled effect estimate [95% CI] and conclusion	SROB across studies	Consistency	Directness	Precision	Outcome reporting bias	Quality of the evidence (GRADE)*
Treatment 1 vs. Treatment 2 (n studies)								
Outcome 1								
Outcome 2								
Outcome 3								
Outcome 4								
Treatment 1 vs. Treatment 3 (n studies)								
Outcome 1								
Outcome 2								
Outcome 3								
Outcome 4								

GRADE= Grading of Recommendations, Assessment, Development, and Evaluation; CI=confidence interval; SROB=summary risk of bias; NA=not applicable

*GRADE categories: high, moderate, low, very low, NA (no evidence)

8.2 Appendix II: Search strategies

Ovid MEDLINE 1946 to August 2013 (searched on 29/08/2013)

1. Crohn Disease/
2. Inflammatory Bowel Diseases/
3. crohn*.tw.
4. Inflammatory bowel disease*.tw.
5. 1 or 2 or 3 or 4
6. ((Enteral or elemental or chemically defined) and (Nutrition$ or diet$ or therap$ or feed$ or formula$)).tw.
7. Enteral Nutrition/
8. Food, Formulated/
9. 6 or 7 or 8
10. (remission* or inactiv* or quiescen* or relaps* or recurr* or maintenan*).tw
11. disease-free survival/
12. 10 or 11
13. 5 and 9 and 12
14. limit 13 to english language

EMBASE 1947 to August 2013 (searched on 29/08/2013)

1. Crohn disease/
2. crohn*.tw.
3. Inflammatory bowel disease*.tw.
4. 1 or 2 or 3
5. ((Enteral or elemental or chemically defined) and (nutrition$ or diet$ or therap$ or feed$ or formula$)).tw.
6. enteric feeding/
7. elemental diet/
8. 5 or 6 or 7
9. (remission* or inactiv* or quiescen* or relaps* or recurr* or maintenan*).tw.
10. disease free survival/
11. 9 or 10
12. 4 and 8 and 11
13. limit 12 to english language

Ovid MEDLINE In-Process & Other Non-Indexed Citations August 2013 (searched on 29/08/2013

1. crohn*.tw.
2. Inflammatory bowel disease*.tw.
3. 1 or 2
4. ((Enteral or elemental or chemically defined) and (Nutrition$ or diet$ or therap$ or feed$ or formula$)).tw.
5. Enteral Nutrition.tw.
6. Food, Formulated.tw.
7. 4 or 5 or 6
8. (remission* or inactiv* or quiescen* or relaps* or recurr* or maintenan*).tw.
9. disease-free survival.tw.
10. 8 or 9
11. 3 and 7 and 10
12. limit 11 to english language

Science Citation Index and Conference Proceedings via the Web of Science (searched on 29/08/2013)

Topic= (crohn* or Inflammatory bowel disease or Crohn Disease) and (Enteral or elemental or chemically defined or Nutrition* or diet* or therap* or feed* or formula* or Enteral Nutrition or Food, Formulated) and (remission* or inactiv* or quiescen* or relaps* or recurr* or maintenan* or disease-free survival)

Cochrane Library, searched on 04/09/13

#1	MeSH descriptor: [Crohn Disease] this term only
#2	MeSH descriptor: [Inflammatory Bowel Diseases] this term only
#3	(crohn*):ti,ab,kw
#4	(Inflammatory bowel disease*):ti,ab,kw
#5	(#1 or #2 or #3 or #4)
#6	(#1 or #2)
#7	((Enteral or elemental or chemically defined) and (Nutrition$ or diet$ or therap$ or feed$ or formula$)):ti,ab,kw
#8	MeSH descriptor: [Enteral Nutrition] this term only
#9	MeSH descriptor: [Food, Formulated] this term only
#10	(#7 or #8 or #9)
#11	(remission* or inactiv* or quiescen* or relaps* or recurr* or maintenan*):ti,ab,kw
#12	MeSH descriptor: [Disease-Free Survival] this term only
#13	(#11 or #12)
#14	(#5 and #10 and #13)

All Results (61)
Cochrane Reviews (4)
All
Review
Protocol
Other Reviews (5)
Trials (52)
Methods Studies (0)
Technology Assessments (0)
Economic Evaluations (0)
Cochrane Groups (0)

Trial database

WHO ICTRP, searched on 20/09/20138

8 records for 8 trials found for: crohn* and element*
3 records for 3 trials found for: inflammatory bowel disease* and element*
13 records for 12 trials found for: crohn* and enteral*
2 records for 2 trials found for: inflammatory bowel disease* and enteral*
Total: 25
Total after duplicates removed: 21
Total after initial sifting by RC: 3
Total after check by AT and TG: 0

UKCRN Study Portfolio

Topic: All

AND

Research summary: inflammatory bowel diseases elemental (All terms)

OR

Research summary: inflammatory bowel disease elemental (All terms)

OR

Research summary: inflammatory bowel diseases enteral (All terms)

OR

Research summary: inflammatory bowel disease enteral (All terms)

OR

Research summary: crohn elemental (All terms)

OR

Research summary: crohn enteral (All terms)

OR

Research summary: crohn’s elemental (All terms)

OR

Research summary: crohn’s enteral (All terms)

Total: 1
Total after sifting by RC: 0

8.3 Appendix III: Full data extraction of included primary study reports

RCTs

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Hanai 2012[50]
Country: Japan
Study design: RCT
Study setting (primary care/specialty clinic/other - specify): specialty clinic
Number of centres: one
Total length of follow up: 24 mo
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To evaluate the efficacy of elemental nutrition versus 6-mercaptopurine as maintenance therapy in Crohn's disease

Participants

Recruitment dates: NR
Total N of patients who received induction therapy: NR
Total N of patients achieving remission after induction therapy: 105
Total N of patients unable to achieve remission after induction therapy: NR
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 10
Total number of patients allocated to maintenance treatment: 95
Inclusion criteria: age ≥18 years who achieved remission (CDAI < 150) within 30 days of entry to this trial
Exclusion criteria: patients with abdominal abscess, stricture (B1 of Vienna and Montreal classification), pregnant women, patients with cardiovascular disorders and history of intolerance to 6-MP
Characteristics of participants (total study sample)
Mean (range or SD) age (years): mean range 29.8-32.5
Women (n [%]): 25/95 [26.3]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: NR
Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 89.9-103.4
CD location (n [%]): Ilio-colic type (59/95 [62.2]), Ileal type (27/95 [28.4]), Colic type (8/95 [8.4])
Type of induction therapy (e.g., medical, surgical): parenteral nutrition (70/95 [73.7]), central venous feeding (25/95 [26.3]), prednisolone (9/95 [9.5]), infliximab (4/95 [4.2]), 6-MP (14/95 [14.7])
Previous surgery (n [%]): 19/95 [20.0]

Intervention

Elemental nutrition group: elemental nutrition
Intervention 2 group: 6-mercaptopurine (MP)
Intervention 3 group: no intervention

Outcomes (study-based)

Primary outcomes (*list*): remission maintenance rate, risk of relapse
Measure of disease activity (clinical, endoscopic): CDAI score
Definition of remission (clinical, endoscopic): CDAI < 150
Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or the need for an additional medication to suppress worsening symptoms)
Definition of mucosal healing (clinical, endoscopic): NR
Post-baseline timings of primary outcome assessment: 6, 12, 18, 24 mo

Number of patients

	Total	Elemental nutrition group	6-MP group	No intervention group
Allocated to treatment	95	32	30	33
Analysed (specify ITT and/or per protocol)	95 (ITT)	32	30	33

(If more than one follow-up, choose and specify the last one)				
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)	11	5	2	4

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental nutrition group	Elental (Ajinomoto, Tokyo) at ≥900 kcal/day, taken via self-inserted feeding tube (2 pts) or by oral intake (32 pts). Restricted diet: patients were allowed an intake of 3.5–4.0 kcal/kg/day from food as recommended by a qualified dietician. Duration: 24 mo	5-aminosalicylic acid (n=NR; 5-ASA, 2250–3000 mg/day) Sulphasalazine (n=NR; 3000 mg/day) Duration: 24 mo
6-MP group	Starting dose 20 mg/day (weight<45 kg) starting dose 30 mg/day (weight ≥45 kg) Within 8–12 weeks of the initial dosing, if 6-TGN level ≤200 pmol/8×10^8 RBC, the dose of 6-MP could be increased by 10mg increments up to a maximum of 80 mg/day. When 6-TGN level reached 450 pmol/8×10^8 RBC, but the patient had not responded, a 5 mg/day increase could be made and the patient was monitored every 2 weeks for efficacy and toxicity or until white blood cell count (WBC) started to decrease.	5-aminosalicylic acid (n=NR; 5-ASA, 2250–3000 mg/day) Sulphasalazine (n=NR; 3000 mg/day) Duration: 24 mo
No intervention group	-	5-aminosalicylic acid (n=NR; 5-ASA, 2250–3000 mg/day) Sulphasalazine (n=NR; 3000 mg/day) Duration: 24 mo

Patient baseline characteristics			
	Elemental nutrition group	**6-MP group**	**No intervention group**
Age (years) Mean (SD)	30.1 (7.7)	32.5 (8.9)	29.8 (10.3)
Sex –female n/N (%)	10/32 (31.2)	7/30 (23.3)	8/33 (24.2)
Weight (kg) Mean (SD)	NR	NR	NR
BMI (kg/m^2) Mean (SD)	NR	NR	NR
Smoking n/N (%)	18/32 (56.2)	15/30 (50.0)	18/33 (54.5)
Previous bowel resection n/N (%)	NR	NR	NR
Duration of CD (months) Mean (SD)	73.2 (69.6)	67.2 (80.4)	58.8 (75.6)

Crohn's Disease Activity Index (CDAI) Mean (SD)	103.4 (21.4)	93.2 (27.8)		89.9 (30.1)
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR		NR
Disease activity other than CDAI (specify)	NR	NR		NR
Mucosal ulceration n/N (%)	NR	NR		NR
Other complications n/N (%)	NR	NR		NR
Efficacy outcomes				
For each timing of assessment please provide a separate table *For scores, extract only total scores* Post-baseline follow-up assessment timing (Specify): 6, 12, 18, 24 mo				
	Elemental nutrition group	**6-MP group**	**No intervention group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)	27/32 (84.4) at 6 mo 20/32 (62.5) at 12 mo 14/32 (46.9) at 24 mo	24/30 (80.0) at 6 mo 20/30 (66.7) at 12 mo 17/30 (56.7) at 24 mo	23/33 (69.6) at 6 mo 15/33 (45.5) at 12 mo 7/33 (21.2) at 24 mo	**(1 vs. 2)** RR=1.05 (0.83, 1.33) at 6 mo; calculated RR=0.93 (0.64, 1.35) at 12 mo; calculated RR=0.77 (0.46, 1.27) at 24 mo; calculated **(1 vs. 3)** RR=1.21 (0.92, 1.58) at 6 mo; calculated RR=1.37 (0.86, 2.17) at 12 mo; calculated RR=2.06 (1.00, 4.43) at 24 mo; calculated
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NR	NA
Risk of relapse or recurrence n/N (%)	12/32 (37.5) at 24 mo	7/30 (23.3) at 24 mo	21/33 (63.6) at 24 mo	**(1 vs. 2)** RR=1.61 (0.73, 3.53) at 24 mo; calculated **(1 vs. 3)** RR=0.58 (0.35, 0.98) at 24 mo; calculated
Time to relapse (months) Mean (SD) or 95% CI	NR	NR	NR	NA
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NR	**(1 vs. 2)** p=0.83 [NS] at 6 mo p=0.54 [NS] at 12 mo p=0.41 [NS] at 18 mo p=0.31 [NS] at 24

				mo **<u>(1 vs. 3)</u>** p=0.19 [NS] at 6 mo p=0.17 [NS] at 12 mo p=0.04 [SS] at 18 mo p=0.03 [SS] at 24 mo
Patients achieving mucosal healing n/N (%)	NR	NR	NR	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NR	NA
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NR	NA
The Short Form Health Survey (SF-12) Mean (SD) 95% CI	NR	NR	NR	NA
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NR	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NR	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NR	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NR	NA
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NR	NA
Height gain (cm) Mean (SD) 95% CI	NR	NR	NR	NA
Linear growth rate (mean height-for-age Z-score)	NR	NR	NR	NA
Adherence n/N (%)	NR	NR	NR	NA
Need for surgery n/N (%)	1/32 (3.1)	1/30 (3.1)	1/33 (3.0)	**<u>1 vs. 2</u>** p>0.99 [NS] Fisher's exact test; RR=0.93 (0.06, 14.32) calculated **<u>1 vs. 3</u>** p>0.99 [NS] Fisher's exact test; RR=1.03 (0.06, 15.79)

				calculated
Steroid dose tapering n/N (%)	NR	NR	NR	NA
Withdrawal from steroids n/N (%)	NR	NR	NR	NA
Adverse events due to treatment n/N (%)	0/32 (0.0)	2/30 (6.6) [elevated AST] 1/30 (3.1) [hair loss]	1/33 (3.0) [elevated amylase]	-
Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]				
	Elemental nutrition group	**6-MP group**	**No intervention group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)	NR	NR	NR	NA
Delay in pubertal development n/N (%)	NR	NR	NR	NA
Bowel obstruction	NR	NR	NR	NA
Fistulae	NR	NR	NR	NA
Abscess	0/32 (0.0)	1/30 (3.1)	0/33 (0.0)	-
Colon/bowel cancer	NR	NR	NR	NA
Intestinal infection	NR	NR	NR	NA
Others (Specify)	NR	NR	NR	NA
Authors conclusion				
Elemental nutrition as maintenance therapy in Crohn's disease patients was as effective as 6-mercaptopurine. Elental should be useful for long-term maintenance therapy in Crohn's disease				
Reviewer's conclusion				
At all follow up points (6, 12, and 24 mo), pts on elemental nutrition and 6-MP experienced similar rates of remission maintenance and relapse; at 6 and 12 mo of follow-up, the rates for remission maintenance and relapse were not different between the elemental nutrition and the control (no intervention) groups. However, at 24 mo of follow up, the elemental nutrition group had significantly greater remission maintenance rates and reduced risk of relapse compared to the control (no intervention) group				

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)
AST; Serum Aspartate transaminase, 6-TGN level; 6-Thioguanine nucleotide

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Takagi 2006,[52]Takagi 2009,[54] Takagi 2006,[53]
Country: Japan
Study design: RCT
Study setting (primary care/specialty clinic/other - specify): specialty clinic
Number of centres: two
Total length of follow up: 24 mo
Funding (government/private/manufacturer/other - specify): no external funding received

Aim of the study

To compare relapse rates in pts with inactive CD receiving half elemental nutrition (elemental nutrition + unrestricted diet) vs. no intervention (unrestricted diet)

Participants

Recruitment dates: December 2002-June 2005
Total N of patients who received induction therapy: 82
Total N of patients achieving remission after induction therapy: 56
Total N of patients unable to achieve remission after induction therapy: 26
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 31
Total number of patients allocated to maintenance treatment: 51
Inclusion criteria: CD pts if they had just undergone induction of remission
Exclusion criteria: NR
Characteristics of participants (total study sample)
Mean (range or SD) age (years): mean range 28.9-30.8
Women (n [%]): 14/51 [27.4]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: clinically, endoscopically, radiologically and/or histologically (diagnostic criteria as defined by the Ministry of Health, Labour and Welfare of Japan)
Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 86.4-101.8
CD location (n [%]): small bowel only (15/51 [29.4]), colon only (9/51 [17.6]), small bowel and colon (27/51 [53.0])
Type of induction therapy (e.g., medical, surgical): elemental enteral nutrition 22/51 [43.1] (1800–2100 kcal/day) for 6–8 weeks; total parenteral nutrition 25/51 [49.0] (1500–2100 kcal/day) for 6–8 weeks; oral/IV prednisolone 1/51 [2.0] (40 mg/day, then tapered down every 2 weeks by 5–10 mg); 5 mg/kg IV infliximab 3/51 [5.9], and/or surgery (5/51 [7.9])
Previous surgery (n [%]): 22/51 [43.1]

Intervention

Elemental nutrition group: half elemental nutrition (i.e., elemental nutrition + unrestricted diet)
Intervention 2 group: free (unrestricted) diet [no intervention]
Intervention 3 group: NA

Outcomes (study-based)

Primary outcomes (*list*): cumulative rate of relapse
Measure of disease activity (clinical, endoscopic): CDAI
Definition of remission (clinical, endoscopic): CDAI<150
Definition of relapse/recurrence (clinical, endoscopic): CDAI > 200, or the need for therapy to induce remission
Definition of mucosal healing (clinical, endoscopic): NR
Post-baseline timings of primary outcome assessment: 6, 12, 18, 24 mo

Number of patients

	Total	**Elemental nutrition group**	**Free/unrestricted diet group (no intervention)**	**Intervention 3 group**
Allocated to treatment	51	26	25	NA
Analysed (specify ITT and/or per protocol) (If more than one follow-up, choose and specify the last	51 (ITT)	26	25	NA

one)				
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)	11	6 (non-adherent; discontinuation of elemental nutrition)	5 (non-adherent; cross-intervention)	NA

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental nutrition group	Pts had to take half the amount of their daily allowance of calories by elemental nutrition and the remaining half by usual unrestricted meals. Elental (AJINOMOTO PHARMA Co., Tokyo, Japan) through a self-inserted tube and/or by oral intake. Total energy content of 375 kcal 100 g. The dosage was 900–1200 kcal/d (240–320 g as powder, 900–1200 mL as solution in water, 3–4 sachets) Unrestricted diet Duration: NR	Mesalazine 2250–3000 mg/day/p.o. (26/26 [100]) Azathioprine 50 mg/day/p.o. (2/26 [7.6])
Free/unrestricted diet group (no intervention)	Unrestricted diet; pts took all nutrients via their usual un-restricted meals. The energy requirements of individual patients were 35–40 kcal/kg ideal body weight/day.	Mesalazine 2250–3000 mg/day/p.o. (25/25 [100]) Azathioprine 50 mg/day/p.o. (4/25 [16.0])
Intervention 3 group	NA	NA

Patient baseline characteristics			
	Elemental nutrition group	**Free/unrestricted diet group (no intervention)**	**Intervention 3 group**
Age (years) Mean (SD)	30.8 (11.1)	28.9 (8.1)	NA
Sex –female n/N (%)	6/26 (23.1)	8/25 (32.0)	NA
Weight (kg) Mean (SD)	NR	NR	NA
BMI (kg/m^2) Mean (SD)	20.1 (3.1)	20.0 (3.6)	NA
Smoking n/N (%)	NR	NR	NA
Previous bowel resection n/N (%)	11/26 (42.3)	11/25 (44.0)	NA
Duration of CD (months) Mean (SD)	49.2 (50.4)	67.2 (78.0)	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	101.8 (34.1)	86.4 (31.3)	NA
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR	NA

Disease activity other than CDAI (specify)	NR	NR		NA
Mucosal ulceration n/N (%)	Perianal lesions 12/26 (46.1)	Perianal lesions 10/25 (40.0)		NA
Other complications n/N (%)	NR	NR		NA
Efficacy outcomes				
For each timing of assessment please provide a separate table *For scores, extract only total scores* Post-baseline follow-up assessment timing (Specify): 12 mo				
	Elemental nutrition group	**Free/unrestricted diet group (no intervention)**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)	NR	NR	NA	NA
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	9/26 (34.6)	16/25 (64.0)	NA	HR (adjusted)=0.40 (0.16, 0.98) study reported; in favour of elemental nutrition group RR=0.54 (0.29, 0.99) calculated; in favour of elemental nutrition group
Time to relapse (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NA	NA
Patients achieving mucosal healing n/N (%)	NR	NR	NA	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	NA
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF-12)	NR	NR	NA	NA

Mean (SD) 95% CI				
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NA	NA
Other HQOL (Inflammatory Bowel Disease Questionnaire) Mean (SD) 95% CI	Adjusted mean IBDQ score at 13 mo 171.9 (126.4, 217.3)	Adjusted mean IBDQ score at 13 mo 176.7 (142.5, 211.0)	NA	Adjusted mean IBDQ score difference at 13 mo p>0.05 (NS)
Weight (kg) Mean (SD) 95% CI	NR	NR	NA	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NA	p=NR (NS) study reported
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NA	NA
Height gain (cm) Mean (SD) 95% CI	NR	NR	NA	NA
Linear growth rate (mean height-for-age Z-score)	NR	NR	NA	NA
Adherence n/N (%)	20/26 (77.0)	20/25 (80.0)	NA	RR=0.96 (0.72, 1.28) calculated
Need for surgery n/N (%)	NR	NR	NA	NA
Steroid dose tapering n/N (%)	NR	NR	NA	NA
Withdrawal from steroids n/N (%)	NR	NR	NA	NA
Adverse events due to treatment n/N (%)	0/26 (0.0)	0/25 (0.0)	NA	NA
Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]				
	Elemental nutrition group	**Free/unrestricted diet group (no intervention)**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)	0/26	0/25	NA	NA
Delay in pubertal development n/N (%)	0/26	0/25	NA	NA
Bowel obstruction	0/26	0/25	NA	NA
Fistulae	0/26	0/25	NA	NA
Abscess	0/26	0/25	NA	NA
Colon/bowel cancer	0/26	0/25	NA	NA
Intestinal infection	0/26	0/25	NA	NA
Others (Specify)	0/26	0/25	NA	NA
Authors conclusion				

At 24 mo, pts receiving elemental nutrition experienced significantly reduced risk of relapse compared to those on free diet. No differences were detected in quality of life or cost of treatment between the two groups
Reviewer's conclusion
At 24 mo, pts receiving elemental nutrition experienced significantly reduced risk of relapse compared to those on free diet. No differences were detected in quality of life or cost of treatment between the two groups; no adverse events; adherence was similar between the treatment groups; trial terminated at 24 mo for ethical reasons

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Cost table (mean per patient monthly in yen)[54]

	Elemental nutrition group	**Free diet group**	**Between-group difference p value (or 95% CI)**
Crude costs	109,160 (95% CI: 63,240 - 155,090)	68,970 (95% CI: 22,140–115,800)	NR
Age-/sex-adjusted costs	111,540 (95% CI: 66,850–156,240)	66,490 (95% CI: 20,900–112,080)	NR
Multivariate costs*	105,860 (95% CI: 57,380 - 154,340) About $880.00 US	72,400 (95% CI: 22,810–122,000) About $600.00 US	p>0.05 (NS)

Adjusted for age, sex, duration of disease, site, perianal lesions, previous gut operation, frequency of relapse, administration of azathioprine, inductive therapy (+surgery), and mean CDAI at baseline

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Verma 2001[55]
Country: UK
Study design: RCT
Study setting (primary care/specialty clinic/other - specify): specialty clinic
Number of centres: one
Total length of follow up: 24 mo
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To compare safety and efficacy of elemental and polymeric nutrition in terms of the maintenance of remission, relapse, and intolerance

Participants

Recruitment dates:
Total N of patients who received induction therapy: NR
Total N of patients achieving remission after induction therapy: NR
Total N of patients unable to achieve remission after induction therapy: NR
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 4
Total number of patients allocated to maintenance treatment: 33
Inclusion criteria: pts with inactive CD and documented previously steroid dependency for maintaining clinical remission and two previous unsuccessful attempts to withdraw steroid that prompted recurrence during or after 30 d of withdrawal
Exclusion criteria: recurrent small-bowel obstruction due to Crohn strictures, significant sepsis including perianal disease, previous intolerance to enteral feeding or unwilling to give formal written consent
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 40.8 (SD: 2.7), range: 17-76
Women (n [%]): 23/33 [70.7]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: standard clinical, radiological, endoscopic and histological criteria
Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean range 90.4-106.4
CD location (n [%]): small bowel (11/33 [33.3]), colon (10/33 [30.3]), mixed cites (10/33 [30.3]), anastomotic (2/33 [6.0])
Type of induction therapy (e.g., medical, surgical): medical (prednisolone; mean dose 7.0 (0.5) mg/d)
Previous surgery (n [%]): NR

Intervention

Elemental nutrition group: elemental nutrition (EO28)
Intervention 2 group: polymeric nutrition (Fortisip)
Intervention 3 group: NA

Outcomes (study-based)

Primary outcomes (*list*): remission maintenance rate, time to relapse
Measure of disease activity (clinical, endoscopic): clinical (CDAI)
Definition of remission (clinical, endoscopic): clinical (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h)
Definition of relapse/recurrence (clinical, endoscopic): clinical (CDAI ≥200 or increased by 100 points from baseline)
Definition of mucosal healing (clinical, endoscopic): NR
Post-baseline timings of primary outcome assessment: 12 mo

Number of patients

	Total	**Elemental nutrition group**	**Polymeric nutrition group**	**Intervention 3 group**
Allocated to treatment	33	19	14	NA
Analysed (specify ITT and/or per protocol) (If more than one follow-up, choose and	33 (ITT) 27 (PP)	19 (ITT) 13 (PP)	14 (ITT) 14 (PP)	NA

specify the last one)				
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)	6	6	0	NA

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental nutrition group	Orally taken (EO28, Scientific Hospital Supplies Ltd, Liverpool, UK); sachets containing powdered feed mixed with tap water (20 g/100 ml); energy content 76 Kcal per 20g/100 ml; the mean daily intake 730 (range 600–1017) Kcal Unrestricted normal diet Duration: 12 mo	Steroids/prednisolone (n=19; 6.5 (0.8) mg) Azathioprine (n=6; dose: NR) 5ASA (n=3; dose: NR) Duration: 12 mo
Polymeric nutrition group	Orally taken (Fortisip, Nutricia, UK); ready-to-drink cartons (200 ml); energy content 150 Kcal per 100 ml; the mean daily intake 730 (range 600–1017) Kcal Unrestricted normal diet Duration: 12 mo	Steroids/prednisolone (n=14; 7.1 (0.9) mg) Azathioprine (n=8; dose: NR) 5ASA (n=2; dose: NR) Duration: 12 mo
Intervention 3 group	NA	NA

Patient baseline characteristics			
	Elemental nutrition group	**Polymeric nutrition group**	**Intervention 3 group**
Age (years) Mean (SD)	41.7 (5.4)	44.1 (3.2)	NA
Sex –female n/N (%)	13/19 (68.4)	9/14 (64.3)	NA
Weight (kg) Mean (SD)	62.4 (3.4)	71.4 (7.7)	NA
BMI (kg/m^2) Mean (SD)	21.8 (1.2)	24.4 (1.6)	NA
Smoking n/N (%)	NR	NR	NA
Previous bowel resection n/N (%)	NR	NR	NA
Duration of CD (months) Mean (SD)	154.4 (37.2)	123.6 (26.4)	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	106.4 (14.9)	90.4 (17.8)	NA
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR	NA
Disease activity other than CDAI (specify)	NR	NR	NA
Mucosal ulceration	NR	NR	NA

n/N (%)			
Other complications n/N (%)	NR	NR	NA

Efficacy outcomes

For each timing of assessment please provide a separate table
For scores, extract only total scores
Post-baseline follow-up assessment timing (Specify): 12 mo

	Elemental nutrition group	**Polymeric nutrition group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)	8/19 (42.1)	6/14 (42.8)	NA	p=NR (NS) study reported RR=0.98 (0.44, 2.19) calculated
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	8/19 (42.1)	5/14 (35.7)	NA	p=NR (NS) study reported RR=1.18 (0.48, 2.83) calculated
Time to relapse (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NA	NA
Patients achieving mucosal healing n/N (%)	NR	NR	NA	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	NA
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF-12) Mean (SD) 95% CI	NR	NR	NA	NA
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NA	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NA	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NA	NA

Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NA	NA
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NA	NA
Height gain (cm) Mean (SD) 95% CI	NR	NR	NA	NA
Linear growth rate (mean height-for-age Z-score)	NR	NR	NA	NA
Adherence n/N (%)	13/19 (68.4)	14/14 (100.0)		RR=0.68 (0.50, 0.92) calculated; in favour of polymeric nutrition group
Need for surgery n/N (%)	NR	NR	NA	NA
Steroid dose tapering n/N (%)	NR	NR	NA	NA
Withdrawal from steroids n/N (%)	8/19 (42.1)	6/14 (42.8)		p=NR (NS) study reported RR=0.98 (0.44, 2.19) calculated
Adverse events due to treatment n/N (%)	NR	NR	NA	NA

Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]				
	Elemental nutrition group	**Polymeric nutrition group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)	NR	NR	NA	NA
Delay in pubertal development n/N (%)	NR	NR	NA	NA
Bowel obstruction	NR	NR	NA	NA
Fistulae	NR	NR	NA	NA
Abscess	NR	NR	NA	NA
Colon/bowel cancer	NR	NR	NA	NA
Intestinal infection	NR	NR	NA	NA
Others (Specify)	NR	NR	NA	NA

Authors conclusion
The two formulas are similar in maintaining remission rate and risk of relapse, or withdrawal from steroids use
Reviewer's conclusion
The two formulas are similar in maintaining remission rate, risk of relapse, or withdrawal from steroids use

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Non-RCTs

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Hirakawa 1993[51]
Country: Japan
Study design: non randomised controlled trial
Study setting (primary care/specialty clinic/other - specify): primary care
Number of centres: one
Total length of follow up: 48 mo
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To compare the effects of elemental nutrition alone, combination of elemental nutrition and drugs, drugs alone, and no intervention on maintenance of remission in CD pts

Participants

Recruitment dates: NR
Total N of patients who received induction therapy: 84
Total N of patients achieving remission after induction therapy: 67
Total N of patients unable to achieve remission after induction therapy: NR
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): NR
Total number of patients allocated to maintenance treatment: 61
Inclusion criteria: pts with CD in remission
Exclusion criteria: pts with active CD
Characteristics of participants (total study sample)
Mean (range or SD) age (years): mean 21.9-27.0
Women (n [%]): 14/53 [26.4]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: Criteria of the Japanese Society Gastroenterology
Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean 61.6-69.3
CD location (n [%]): small bowel (5/53 [9.4]), large bowel (6/53 [11.3]), small and large bowels (42/53 [79.2])
Type of induction therapy (e.g., medical, surgical): elemental nutrition (25/53 [47.1]), elemental nutrition and drugs (23/53 [43.4]), drugs alone (5/53 [9.4])
Previous surgery (n [%]): NR

Intervention

Elemental nutrition group: elemental nutrition
Intervention 2 group: elemental nutrition + drugs (sulfasalazine 3g/d or prednisolone 10mg/d)
Intervention 3 group: drugs (sulfasalazine 3g/d or prednisolone 10mg/d)
Intervention 4 group: No intervention

Outcomes (study-based)

Primary outcomes (*list*): cumulative continuous remission rate
Measure of disease activity (clinical, endoscopic): CDAI and International Organization for the Study of Inflammatory Bowel Disease (IOIBD) scores
Definition of remission (clinical, endoscopic): IOIBD score (value: NR) and normal values of ESR and CRP
Definition of relapse/recurrence (clinical, endoscopic): recurrence of subjective/objective symptoms (increase of the IOIBD score by ≥2, enhanced ESR, and positive CRP)
Definition of mucosal healing (clinical, endoscopic): NR
Post-baseline timings of primary outcome assessment: 12, 24, 36, and 48 mo

Number of patients

	Total	**Elemental nutrition group**	**Elemental nutrition + drugs group**	**Drugs group**	**No intervention group**
Allocated to treatment	61	25	22	8	6
Analysed (specify ITT and/or per protocol) (If more than	(n=53) Per protocol	22	17	8	6

one follow-up, choose and specify the last one)					
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)	8	3	5	0	0

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental nutrition group	>30 kcal/kg IBW/d through nasoenteral tube as home elemental enteral hyperalimentation Actual consumption: 35.2 (SD=4.8) kcal/kg IBW/d Brand: NR Duration of EN: NR Restricted diet additionally	-
Elemental nutrition + drugs group	>30 kcal/kg IBW/d through nasoenteral tube as home elemental enteral hyperalimentation Actual consumption: 31.8 (SD=4.4) kcal/kg IBW/d Brand: NR Duration of EN: NR Sulfasalazine 3g/d (n=10) prednisolone 10mg/d (n=7) Duration: NR Restricted diet additionally	NR
Drugs group	Sulfasalazine 3g/d (n=10) prednisolone 10mg/d (n=7) Duration: NR Restricted diet	NR
No intervention group	Restricted diet	-

Patient baseline characteristics				
	Elemental nutrition group	**Elemental nutrition + drugs group**	**Drugs group**	**No intervention group**
Age (years) Mean (SD)	27.0 (7.4)	26.6 (2.4)	21.9 (2.6)	25.7 (5.0)
Sex –female n/N (%)	3/22 (13.6)	6/17 (35.3)	3/8 (37.5)	2/6 (33.3)
Weight (kg) Mean (SD)	NR	NR	NR	NR
BMI (kg/m^2) Mean (SD)	NR	NR	NR	NR
Smoking n/N	NR	NR	NR	NR

(%)					
Previous bowel resection n/N (%)	NR	NR	NR		NR
Duration of CD (months) Mean (SD)	NR	NR	NR		NR
Crohn's Disease Activity Index (CDAI) Mean (SD)	61.6 (29.2)	56.0 (26.6)	68.5 (30.2)		69.3 (52.1)
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR	NR		NR
Disease activity other than CDAI (IOIBD)	0.2 (0.5)	0.3 (0.5)	0.3 (0.5)		0.3 (0.5)
Mucosal ulceration n/N (%)	NR	NR	NR		NR
Other complications n/N (%)	Fistula 8/22 (36.4)	Fistula 9/17 (53.0)	Fistula 3/8 (37.5)		Fistula 1/6 (16.6)
Efficacy outcomes					
For each timing of assessment please provide a separate table *For scores, extract only total scores* Post-baseline follow-up assessment timing (Specify): 12, 24, and 48 mo					
	Elemental nutrition group	**Elemental nutrition + drugs group**	**Drugs group**	**No intervention group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)	NR	NR	NR	NR	NA
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NR	NR	NA
Risk of relapse or recurrence n/N (%)	NR	NR	NR	NR	NA
Time to relapse (months) Mean (SD) or 95% CI	NR	NR	NR	NR	NA
Survival rate (% patients in	12 mo: 94% (NR) 24 mo: 63% (NR)	75% (NR) 66% (NR)	63% (NR) 42% (NR)	50% (NR) 33% (NR)	**At 48 mo** p<0.05 (1 vs. 3)

remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	48 mo: 63% (NR)	66% (NR)	0% (NR)	0% (NR)	SS p<0.01 (1 vs. 4) SS p<0.05 (2 vs. 4) SS p≥0.05 (2 vs. 3) NS p≥0.05 (1 vs. 2) NS
Patients achieving mucosal healing n/N (%)	NR	NR	NR	NR	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NR	NR	NA
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NR	NR	NA
The Short Form Health Survey (SF-12) Mean (SD) 95% CI	NR	NR	NR	NR	NA
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NR	NR	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NR	NR	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NR	NR	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NR	NR	NA
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NR	NR	NA
Height gain (cm) Mean (SD) 95% CI	NR	NR	NR	NR	NA

Linear growth rate (mean height-for-age Z-score)	NR	NR	NR	NR	NA
Adherence n/N (%)	22/25 (88.0)	17/22 (77.3)	8/8 (100.0)	6/6 (100.0)	Fisher's exact test p=0.55 [1 vs. 2] NS p=0.84 [1 vs. 3] NS p>0.99 [1 vs. 4] NS p=0.37 [2 vs. 3] NS p=0.53 [2 vs. 4] NS calculated
Need for surgery n/N (%)	NR	NR	NR	NR	NA
Steroid dose tapering n/N (%)	NR	NR	NR	NR	NA
Withdrawal from steroids n/N (%)	NR	NR	NR	NR	NA
Adverse events due to treatment n/N (%)	NR	NR	NR	NR	NA
Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]					
	Elemental nutrition group	**Elemental nutrition + drugs group**	**Drugs group**	**No intervention group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)	NR	NR	NR	NR	NA
Delay in pubertal development n/N (%)	NR	NR	NR	NR	NA
Bowel obstruction	NR	NR	NR	NR	NA
Fistulae	NR	NR	NR	NR	NA
Abscess	NR	NR	NR	NR	NA
Colon/bowel cancer	NR	NR	NR	NR	NA
Intestinal infection	NR	NR	NR	NR	NA
Others (Specify)	NR	NR	NR	NR	NA
Authors conclusion					
At 1, 2, and 4 yrs of follow-up, both groups of elemental nutrition (with/without drugs) experienced significantly greater rates of remission maintenance compared to no intervention; elemental nutrition alone (but not elemental nutrition + drug) was more effective than drug alone					
Reviewer's conclusion					

Long term administration of elemental nutrition with or without drugs in pts with CD resulted in improved rates of maintenance of remission compared with no intervention; there was no significant difference in rates of remission maintenance between the two elemental nutrition or two drug groups

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Name of first reviewer: alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Verma 2000[56]
Country: UK
Study design: non-randomised controlled trial
Study setting (primary care/specialty clinic/other - specify): specialty clinic
Number of centres: one
Total length of follow up: 24 mo
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To evaluate clinical effectiveness of adding an elemental nutrition taken orally to normal food for maintaining remission in patients with quiescent CD over 12 months

Participants

Recruitment dates: NR
Total N of patients who received induction therapy: 46
Total N of patients achieving remission after induction therapy: 39
Total N of patients unable to achieve remission after induction therapy: 7
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): 7
Total number of patients allocated to maintenance treatment: 39
Inclusion criteria: pts with quiescent disease defined by the absence of bowel symptoms and CDAI<150 who had been treated with either elemental nutrition or prednisolone as an induction therapy within preceding 12 months
Exclusion criteria: CDAI>150, sepsis, bowel strictures leading to recurrent attacks of small bowel obstruction or previous intolerance to enteral feeding
Characteristics of participants (total study sample)
Mean (range or SD) age (years): mean 39.2 – 42.0 yrs
Women (n [%]): 27 [69.2]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: standard clinical, endoscopic, radiological, and when possible, histological criteria
Mean Crohn's Disease Activity Index (CDAI) (range or SD): mean 94.6 – 112.8
CD location (n [%]): small bowel (17[43.6]), large bowel (n=10[25.6]), mixed (n=9[23.0]), anastomatic (n=3[7.6])
Type of induction therapy (e.g., medical, surgical): medical (prednisolone, azathioprine, 5-ASA)
Previous surgery (n [%]): 12 [100]

Intervention

Elemental nutrition group: elemental nutrition **"**EO28 Extra" (with normal unrestricted diet)
Intervention 2 group: no intervention (i.e., normal unrestricted diet)
Intervention 3 group: NA

Outcomes (study-based)

Primary outcomes (*list*): maintenance of clinical remission at 12 mo, withdrawal from steroids, and duration of remission at 24 mo
Measure of disease activity (clinical, endoscopic): CDAI
Definition of remission (clinical, endoscopic): CDAI<150
Definition of relapse/recurrence (clinical, endoscopic): increase in CDAI by >100 points since baseline or final CDAI >150 points; need of surgery; increased doses of steroids
Definition of mucosal healing (clinical, endoscopic): NR
Post-baseline timings of primary outcome assessment: 1, 3, 6, 9, 12, and 24 mo

Number of patients

	Total	**Elemental nutrition group**	**No intervention group**	**Intervention 3 group**
Allocated to treatment	39	21	18	NA
Analysed (specify ITT and/or per protocol) (If more than one follow-up, choose and specify the last one)	35	17 (per protocol) 21 (ITT)	18	NA
Losses to follow-		4	0	NA

up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)				

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental nutrition group	EO28 Extra powder containing 443 kcal energy, mixed with water and taken orally in three separate portions daily; mean intake (768.5, SD: 50.6 kcal/d) Duration: 12 mo In addition to normal diet	Prednisolone (mean range: 10.5-17.5 mg/d) azathioprine (dose: NR) 5-ASA (dose: NR) Duration: 12 mo
Intervention 2 group	No intervention (i.e., normal diet) Duration: 12 mo	Prednisolone (mean: 13.4 mg/d) azathioprine (dose: NR) 5-ASA (dose: NR) Duration: 12 mo
Intervention 3 group	NA	NA

Patient baseline characteristics			
	Elemental nutrition group	**No intervention group (i.e., normal diet)**	**Intervention 3 group**
Age (years) Mean (SD)	39.2 (3.9)	42.0 (3.3)	NA
Sex –female n/N (%)	14/21 (66.6)	13/18 (72.2)	NA
Weight (kg) Mean (SD)	59.4 (2.9)	62.7 (2.8)	NA
BMI (kg/m^2) Mean (SD)	20.0 (2.2)	22.9 (0.9)	NA
Smoking n/N (%)	NR	NR	NA
Previous bowel resection n/N (%)	NR	NR	NA
Duration of CD (months) Mean (SD)	60.3 (18.4)	91.0 (14.8)	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	112.8 (11.5)	94.6 (7.1)	NA
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR	NA
Disease activity other than CDAI (specify)	NR	NR	NA
Mucosal ulceration n/N (%)	NR	NR	NA
Other complications n/N (%)	NR	NR	NA

Efficacy outcomes				
For each timing of assessment please provide a separate table *For scores, extract only total scores* Post-baseline follow-up assessment timing (Specify): 12 mo				
	Elemental nutrition group	**No intervention group (i.e., normal diet)**	**Intervention 3 group**	**Between-group difference**

				p value (or 95% CI)*
Patients remaining in remission n/N (%)	10/21 (47.6)	4/18 (22.2)	NA	p=0.0003 (SS) RR=2.14 (0.81, 5.67), p=0.18 (NS) calculated
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	7/21 (33.3)	14/18 (77.7)	NA	p<0.00001 (SS) RR=0.50 (0.25, 0.98) calculated
Time to relapse (months) Mean (SD) or 95% CI	7.4 (0.9)	6.2 (0.4)	NA	NR (study report) MD=1.2 (0.35, 2.04), p=0.012 (SS) calculated
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NA	NA
Patients achieving mucosal healing n/N (%)	NR	NR	NA	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	NA
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF-12) Mean (SD) 95% CI	NR	NR	NA	NA
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NA	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NA	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NA	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NA	NA
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NA	NA
Height gain (cm)	NR	NR	NA	NA

Mean (SD) 95% CI				
Linear growth rate (mean height-for-age Z-score)	NR	NR	NA	NA
Adherence n/N (%)	17/21 (80.9)	18/18 (100.0)	NA	NR (study report) RR=0.81 (0.65, 0.99) calculated; in favour of No intervention group
Need for surgery n/N (%)	NR	NR	NA	NA
Steroid dose tapering n/N (%)	10/21 (47.6)	4/18 (22.2)	NA	NR (study report) RR=2.14 (0.80, 5.67) (NS) calculated
Withdrawal from steroids n/N (%)	4/21 (19.0)	0/18 (0.0)	NA	NR
Adverse events due to treatment n/N (%)	NR	NR	NA	NA
Complications - Number (%) of patients with an event **[if more than one follow-up, choose and specify the last follow up]**				
	Elemental nutrition group	**No intervention group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)	NR	NR	NA	NA
Delay in pubertal development n/N (%)	NR	NR	NA	NA
Bowel obstruction	NR	NR	NA	NA
Fistulae	NR	NR	NA	NA
Abscess	NR	NR	NA	NA
Colon/bowel cancer	NR	NR	NA	NA
Intestinal infection	NR	NR	NA	NA
Others (Specify)	NR	NR	NA	NA
Authors conclusion				
Over 12 mo, the EN group had higher maintenance remission rate vs. no intervention (usual diet) group				
Reviewer's conclusion				
Pts receiving EN experienced greater remission rates, longer time to relapse, reduced rates of replace, but similar CDAI, BMI, or weight compared to the control group at 12 mo of FU; results for steroid tapering/withdrawals, adherence, and intolerance are inconclusive due to small sample number of events or sample size				

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Yamamoto 2007a,[30]; Yamamoto 2013,[59];Yamamoto 2013,[60]
Country: Japan
Study design: non-randomised controlled trial
Study setting (primary care/specialty clinic/other - specify): specialty clinic
Number of centres: one
Total length of follow up: 12 mo
Funding (government/private/manufacturer/other - specify): other (no external funding received)

Aim of the study

To examine if long-term elemental nutrition infusion along with low fat diet is useful in reducing clinical and endoscopic recurrence rates after resection for CD

Participants

Recruitment dates: NR
Total N of patients who received induction therapy: NR
Total N of patients achieving remission after induction therapy: NR
Total N of patients unable to achieve remission after induction therapy: NR
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): NR
Total number of patients allocated to maintenance treatment: 40
Inclusion criteria: patients with endoscopic and histological diagnosis of CD, aged 15-75 yrs who had resection for ileal and ileocolonic (including ileocaecal) CD; received EN therapy including elemental nutrition infusion at least once before operation; agreed to continue assigned treatment (with or without enteral nutrition) for more than 1 year after operation
Exclusion criteria: Patients with colonic Crohn's disease alone or with diffuse small bowel Crohn's disease
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 32.0 (17.0)
Women (n [%]): 14/40 [35.0]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: endoscopic and histological (no specific criteria reported)
Mean Crohn's Disease Activity Index (CDAI) (range or SD): NR
CD location (n [%]): Terminal ileum (12/40 [30.0]), terminal ileum and colon (20/40 [50.0]), Ileocolonic anastomosis (8/40 [20.0])
Type of induction therapy (e.g., medical, surgical): bowel resection (40/40 [100.0]), corticosteroids (37/40 [92.5]), pentasa (32/40 [77.5])
Previous surgery (n [%]): 8/40 [20.0]

Intervention

Elemental nutrition group: elemental nutrition (with restricted food diet)
Intervention 2 group: no intervention (i.e., normal unrestricted diet)
Intervention 3 group: NA

Outcomes (study-based)

Primary outcomes (*list*): clinical and endoscopic recurrence
Measure of disease activity (clinical, endoscopic): clinical (CDAI score), endoscopic (Rutgeerts score)
Definition of remission (clinical, endoscopic): CDAI<150 (clinical), Rutgeerts score<2 (endoscopic)
Definition of relapse/recurrence (clinical, endoscopic): clinical (at 6, 12 mo: CDAI≥150; at 60 mo: CDAI≥200), endoscopic (Rutgeerts score≥2)
Definition of mucosal healing (clinical, endoscopic): NR
Post-baseline timings of primary outcome assessment: 6 and 12 mo

Number of patients

	Total	Elemental nutrition group	No intervention group	Intervention 3 group
Allocated to treatment	40	20	20	NA
Analysed (specify ITT and/or per protocol) (If more than one follow-up, choose and	40 (ITT)	20	20	NA

specify the last one)				
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)	0	0	0	NA

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental nutrition group	Elental (Ajinomoto, Tokyo, Japan) with the calorie density of 1 kcal/mL with an osmolarity of 760 mOsm/L. Infused at home nasogastrically via self-intubated tube in the night-time 1 week after operation. The concentration of the elemental nutrition was gradually increased from one-third to the full strength over 10 days (adaptation phase) to reduce side effects, such as diarrhoea and abdominal colic. After the adaptation phase, a maintenance dose at the full strength was administered in the night-time (for 6–10 h). The volume of the elemental nutrition infused per night was 1200–1800 mL Restricted food diet: in the daytime, low fat foods (20–30 g/day) were taken according to the instructions of their dieticians. The daily calorie intake: 35–40 kcal/kg body weight; about half of the calorie was obtained from the elemental nutrition therapy Duration at least 12 mos	Pentasa 3000 mg/day as a prophylactic medication No corticosteroid, immunosuppressive drugs, or infliximab except patients who relapsed
No intervention group	No elemental nutrition, only normal unrestricted diet Duration > 12 mos	Pentasa 3000 mg/day as a prophylactic medication No corticosteroid, immunosuppressive drugs, or infliximab except patients who relapsed
Intervention 3 group	NA	NA

Patient baseline characteristics			
	Elemental nutrition group	**No Intervention group**	**Intervention 3 group**
Age (years) Mean (SD)	31.0 (16.5)	33.0 (17.4)	NA
Sex –female n/N (%)	8/20 (40.0)	6/20 (30.0)	NA
Weight (kg) Mean (SD)	NR	NR	NA
BMI (kg/m^2) Mean (SD)	NR	NR	NA
Smoking n/N (%)	2/20 (10.0)	2/20 (10.0)	NA
Previous bowel resection n/N (%)	20/20 (100.0)	20/20 (100.0)	NA
Duration of CD (months)	37.0 (31.7)	39.0 (36.7)	NA

Mean (SD)			
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR	NA
Disease activity other than CDAI (specify)	NR	NR	NA
Mucosal ulceration n/N (%)	NR	NR	NA
Other complications n/N (%)	Diarrhoea, abdominal distension or colic in most pts (n/N: NR)	NR	NA

Efficacy outcomes

For each timing of assessment please provide a separate table
For scores, extract only total scores
Post-baseline follow-up assessment timing (Specify): 6, 12, 60 mo

	Elemental nutrition group	**No Intervention group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)	12 mo: 19/20 (95.0)	12 mo: 13/20 (65.0)	NA	p=NR RR=1.46 (1.04, 2.05) calculated; in favour of elemental group
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	<u>Clinical</u> 12 mo: 1/20 (5.0) 60 mo: 6/20 (30.0) <u>Endoscopic</u> 6 mo: 5/20 (25.0) 12 mo: 6/20 (30.0) 60 mo: 9/16 (56.2)	<u>Clinical</u> 12 mo: 7/20 (35.0) 60 mo: 12/20 (60.0) <u>Endoscopic</u> 6 mo: 8/20 (40.0) 12 mo: 14/20 (70.0) 60 mo: 14/17 (82.3)		<u>Clinical at 12 mo</u> p=0.048 (SS) study reported; RR=0.14 (0.02, 1.00) calculated; in favour of elemental group <u>Clinical at 60 mo</u> p=0.11 (NS) study reported; RR=0.50 (0.23, 1.07) calculated <u>Endoscopic at 6 mo</u> p=0.50 (NS) study reported; RR=0.62 (0.24, 1.58) calculated <u>Endoscopic at 12 mo</u> p=0.027 (SS) study reported; RR=0.42 (0.20, 0.88) calculated; in favour of elemental group <u>Endoscopic at 60 mo</u> p=0.21 (NS) study reported; RR=0.68

				(0.42, 1.11) calculated
Time to relapse (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NA	NA
Patients achieving mucosal healing n/N (%)	NR	NR	NA	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	NA
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF-12) Mean (SD) 95% CI	NR	NR	NA	NA
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NA	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NA	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NA	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NA	NA
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NA	NA
Height gain (cm) Mean (SD) 95% CI	NR	NR	NA	NA
Linear growth rate (mean height-for-age Z-score)	NR	NR	NA	NA
Adherence n/N (%)	20/20 (100.0) [12 mo] 16/20 (80.0) [60 mo]	20/20 (100.0) [12 mo] 20/20 (100.0) [60 mo]	NA	- [12 mo] RR=0.80 (0.64, 0.99) calculated; in favour of the control group [60 mo]
Need for surgery	1/20 (5.0)	5/20 (25.0)	NA	p=0.18 (NS) study

n/N (%)	[60 mo]	[60 mo]		reported; RR=0.20 (0.02, 1.56) calculated [60 mo]
Steroid dose tapering n/N (%)	NR	NR	NA	NA
Withdrawal from steroids n/N (%)	NR	NR	NA	NA
Adverse events due to treatment n/N (%)	NR	NR	NA	NA
Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]				
	Elemental nutrition group	**No Intervention group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)	NR	NR	NA	NA
Delay in pubertal development n/N (%)	NR	NR	NA	NA
Bowel obstruction	NR	NR	NA	NA
Fistulae	NR	NR	NA	NA
Abscess	NR	NR	NA	NA
Colon/bowel cancer	NR	NR	NA	NA
Intestinal infection	NR	NR	NA	NA
Others (Specify)	NR	NR	NA	NA
Authors conclusion				
The long-term enteral nutritional therapy significantly reduced clinical and endoscopic recurrence after resection for Crohn's disease				
Reviewer's conclusion				
Assignment depended on compliance, i.e., pts with good compliance were assigned to elemental nutrition group and those with low compliance to control group. The long-term enteral nutritional therapy significantly reduced clinical and endoscopic recurrence at 12 mo after resection for Crohn's disease; however, at 60 mo the rates of clinical/endoscopic recurrences as well as the need for operation were not significantly different between the two treatment groups; compliance rates were better in the control group				

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Yamamoto 2007b[57]
Country: Japan
Study design: non-randomised controlled trial
Study setting (primary care/specialty clinic/other - specify): NR
Number of centres: one
Total length of follow up: 12 mo
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To investigate if long-term enteral nutrition (vs. no intervention) is effective in reducing clinical and endoscopic relapse rates and inhibiting mucosal cytokine production in patients with quiescent CD

Participants

Recruitment dates: NR
Total N of patients who received induction therapy: NR
Total N of patients achieving remission after induction therapy: NR
Total N of patients unable to achieve remission after induction therapy: NR
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): NR
Total number of patients allocated to maintenance treatment: 40
Inclusion criteria: patient with endoscopic/histological diagnosis of CD in the terminal ileum and/or the colon; age: 15-75 years; clinical remission (CDAI<150) after medical treatment; the duration from the induction of remission to
entry<8 weeks; patient had experienced enteral nutrition therapy including elemental nutrition infusion at least 1 time before entry; patient agreed to continue with assigned treatment (with or without enteral nutrition) for >1 year; and patient agreed to have ileocolonoscopy with multiple mucosal biopsies even if they did not have any clinical symptoms
Exclusion criteria: diffuse jejunoileal or gastroduodenal; severe anorectal stricture or sepsis; tight bowel strictures or enteric fistulae even though clinical symptoms were quiescent; patient had received corticosteroids, immunosuppressive drugs, or infliximab at entry
Characteristics of participants (total study sample)
Mean (range or SD) age (years): mean 29.0-31.0
Women (n [%]): 13/40 [32.5]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: endoscopic and histological (not specified)
Mean Crohn's Disease Activity Index (CDAI) (range or SD): 97 (56-139)
CD location (n [%]): terminal ileum (15/40 [37.5]), colon (4/40 [10]), terminal ileum and colon (21/40 [52.5])
Type of induction therapy (e.g., medical, surgical): 4 pts (5 mg/kg x 1 or x 3 prednisolone, infliximab), 6 pts (prednisolone with enteral nutrition), 10 pts (prednisolone alone), 20 pts (enteral nutrition alone), 36 pts (Pentasa, 750–3000 mg/day), and the majority of pts required parenteral nutrition at the start of the treatment.
Previous surgery (n [%]): 8/40 [20]

Intervention

Elemental nutrition group: elemental nutrition (with restricted food diet)
Intervention 2 group: no intervention (i.e., normal unrestricted diet)
Intervention 3 group: NA

Outcomes (study-based)

Primary outcomes (*list*): CDAI score, cumulative proportion of pts maintaining clinical remission (CDAI<150), endoscopic severity of disease activity/mucosal inflammation, mucosal cytokine assays
Measure of disease activity (clinical, endoscopic): CDAI (clinical), mucosal inflammation grade by Wardle et al. 1992 [0=macroscopically normal, 1= granular mucosa and contact bleeding, 2= erythematous and edematous mucosa, aphtoid or superficial ulcers, and 3=deep ulcers with slough and inflammatory pseudo polyps] (endoscopic)
Definition of remission (clinical, endoscopic): CDAI<150 (clinical), NR (endoscopic; specific threshold for the mucosal inflammation grade NR)
Definition of relapse/recurrence (clinical, endoscopic): CDAI≥150 (clinical), NR (endoscopic; specific threshold for the mucosal inflammation grade NR)
Definition of mucosal healing (clinical, endoscopic): endoscopic (specific threshold for the mucosal inflammation grade NR)
Post-baseline timings of primary outcome assessment: 0, 6, and 12 mo

Number of patients

	Total	Elemental nutrition group	No intervention group	Intervention 3 group
Allocated to treatment	40	20	20	NA
Analysed (specify ITT and/or per protocol) (If more than one follow-up, choose and specify the last one)	40 (ITT)	20	20	NA
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)	0	0	0	NA
Interventions				
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)			
	Diet		**Co-intervention**	
Elemental nutrition group	Elemental nutrition: Elental (Ajinomoto, Tokyo); one pack contains 80 g of powdered elemental nutrition, dissolved in warm water to give 300 mL of solution; 1200–1800 mL/night infused via self-intubated nasogastric tube every night; patients were advised to take 35–40 kcal/kg ideal body weight daily, and to take approximately half of the calorie from the enteral nutrition Restricted food diet: in the daytime, a low-fat diet (20–30 g/day) was taken in accord with dieticians instructions Duration > 12 mo		Pentasa 3000 mg/day as a prophylactic medication. No corticosteroid, immunosuppressive drugs, or infliximab except patients who relapsed	
No intervention group	No elemental nutrition, only normal unrestricted diet Duration > 12 mo		Pentasa 3000 mg/day as a prophylactic medication. No corticosteroid, immunosuppressive drugs, or infliximab except patients who relapsed	
Intervention 3 group	NA		NA	
Patient baseline characteristics				
	Elemental nutrition group	**No Intervention group**		**Intervention 3 group**
Age (years) Mean (SD)	29.0 (17.4)	31.0 (20.1)		NA
Sex –female n/N (%)	6/20 (30.0)	7/20 (35.0)		NA
Weight (kg) Mean (SD)	51.1 (8.5)	48.9 (7.6)		NA
BMI (kg/m^2) Mean (SD)	19.2 (1.3)	19.1 (1.8)		NA
Smoking n/N (%)	2/20 (10.0)	4/20 (20.0)		NA
Previous bowel	4/20 (20.0)	4/20 (20.0)		NA

resection n/N (%)			
Duration of CD (months) Mean (SD)	32.0 (35.3)	36.0 (38.9)	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	101.0 (28.2)	92.0 (21.5)	NA
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR	NA
Disease activity other than CDAI (endoscopic mucosal inflammation grade 0-3)	Grade 0: 8/20 (40.0) Grade 1: 7/20 (35.0) Grade 2: 3/20 (15.0) Grade 3: 2/20 (10.0)	Grade 0: 9/20 (45.0) Grade 1: 7/20 (35.0) Grade 2: 2/20 (10.0) Grade 3: 2/20 (10.0)	NA
Mucosal ulceration n/N (%)	NR (see above endoscopic mucosal inflammation grade)	NR (see above endoscopic mucosal inflammation grade)	NA
Other complications n/N (%)	Diarrhea, abdominal distention, or colic in most pts (n/N: NR)	NR	NA

Efficacy outcomes

For each timing of assessment please provide a separate table
For scores, extract only total scores
Post-baseline follow-up assessment timing (Specify): 12 mo

	Elemental nutrition group	**No Intervention group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)	15/20 (75.0)	7/20 (35.0)	NA	P=0.01 study reported SS RR=2.14 (1.12, 4.10) SS calculated; in favour of elemental nutrition group
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	5/20 (25.0)	13/20 (65.0)	NA	OR=0.20 p=0.03 (study reported) 95% CI (0.04, 0.70) calculated RR=0.38 (0.16, 0.87) calculated (SS) in favour of elemental nutrition group
Time to relapse (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Survival rate (% patients in remission	NR	NR	NA	p=0.01 (SS) in favour of elemental nutrition

who have not relapsed) (Kaplan-Meier estimate and 95% CI)				group
Patients achieving mucosal healing n/N (%)	Grade 0: 6/20 (30.0)	Grade 0: 2/18 (11.1)	NA	RR=2.70 (0.62, 11.72) NS calculated
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	p=0.04 (SS) in favour of elemental nutrition group
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF-12) Mean (SD) 95% CI	NR	NR	NA	NA
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NA	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NA	NA
Weight (kg) Mean (SD) 95% CI	NR	NR	NA	NS (p>0.05)
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NA	NA
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NA	SS (p<0.05) in favour of elemental nutrition group
Height gain (cm) Mean (SD) 95% CI	NR	NR	NA	NA
Linear growth rate (mean height-for-age Z-score)	NR	NR	NA	NA
Adherence n/N (%)	18/20 (90.0)	20/20 (100.0)	NA	p=0.48 Fisher test (NS)
Need for surgery n/N (%)	0/20 (0.0)	2/20 (10.0)	NA	NR
Steroid dose tapering n/N (%)	NA	NA	NA	NA
Withdrawal from steroids n/N (%)	NA	NA	NA	NA
Adverse events due to treatment n/N (%)	NR	NR	NA	NA
Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]				
	Elemental nutrition group	**No Intervention group**	**Intervention 3 group**	**Between-group difference p value**

				(or 95% CI)*
Impaired growth n/N (%)	NR	NR	NA	NA
Delay in pubertal development n/N (%)	NR	NR	NA	NA
Bowel obstruction	NR	NR	NA	NA
Fistulae	NR	NR	NA	NA
Abscess	NR	NR	NA	NA
Colon/bowel cancer	NR	NR	NA	NA
Intestinal infection	NR	NR	NA	NA
Others (Specify)	NR	NR	NA	NA
Authors conclusion				
Long-term enteral nutrition in patients with quiescent CD has a clear suppressive effect on clinical and endoscopic disease activities and the mucosal inflammatory cytokine levels				
Reviewer's conclusion				
Assignment depended on compliance, i.e., pts with good compliance were assigned to elemental nutrition group and those with low compliance to control group. The maintenance rates of clinical remission, relapse rates, and CDAI scores were significantly better in the elemental nutrition vs. control group after 12 mos of follow-up				

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Tara Gurung

Study details

First author surname year of publication: Yamamoto 2010[58]
Country: Japan
Study design: non-randomised controlled trial
Study setting (primary care/specialty clinic/other - specify): specialty clinic
Number of centres: one
Total length of follow up: 14 mo
Funding (government/private/manufacturer/other - specify): NR

Aim of the study

To assess the efficacy of EN on the maintenance rate of clinical remission in patients with quiescent CD receiving infliximab as maintenance therapy

Participants

Recruitment dates: NR
Total N of patients who received induction therapy: NR
Total N of patients achieving remission after induction therapy: 56
Total N of patients unable to achieve remission after induction therapy: NR
Total N of patients excluded before start of maintenance therapy (e.g., in relapse, lost to follow up): NR
Total number of patients allocated to maintenance treatment: 56
Inclusion criteria: patients diagnosed with CD who had achieved clinical remission (CDAI<150 after infliximab induction therapy) with time from the induction of remission to entry ≤2 weeks; patients who had experienced EN therapy including elemental nutrition infusion at least one time before entry; and patients who agreed to continue with the assigned treatment (with or without concomitant enteral nutrition) for 56 weeks.
Exclusion criteria: patients who had severe anorectal involvement; patients who had tight bowel strictures or enteric fistulae even if clinical symptoms were quiescent
Characteristics of participants (total study sample)
Mean (range or SD) age (years): 32 (NR)
Women (n [%]): 20/56 [35.7]
Race/ethnicity (n [%]): NR
Diagnostic criteria for CD: NR
Mean Crohn's Disease Activity Index (CDAI) (range or SD): 102.2 (NR)
CD location (n [%]): small bowel (22/56 [39.3]), small bowel and colon (34/56 [60.7])
Type of induction therapy (e.g., medical, surgical): medical (infliximab 5 mg/kg)
Previous surgery (n [%]): bowel resection (19/56 [34.0%])

Intervention

Elemental nutrition group: elemental nutrition + infliximab 5 mg/kg + restricted low fat diet
Intervention 2 group: Infliximab 5 mg/kg + unrestricted low fat diet
Intervention 3 group: NA

Outcomes (study-based)

Primary outcomes (*list*): cumulative proportion of pts maintaining clinical remission, CDAI score
Measure of disease activity (clinical, endoscopic): CDAI
Definition of remission (clinical, endoscopic): CDAI < 150
Definition of relapse/recurrence (clinical, endoscopic): CDAI > 150
Definition of mucosal healing (clinical, endoscopic): NR
Post-baseline timings of primary outcome assessment: baseline, 8, 16, 24, 32, 40, 48, and 56 wks

Number of patients

	Total	**Elemental nutrition + infliximab group**	**Infliximab group**	**Intervention 3 group**
Allocated to treatment	56	32	24	NA
Analysed (specify ITT and/or per protocol) (If more than one follow-up, choose and specify the last	56 (ITT)	32	24	NA

one)				
Losses to follow-up/drop out/sample attrition (If more than one follow-up, choose and specify the last one)	0	0	0	NA

Interventions		
	Description (e.g., formula manufacturer, calorie content, type, mode, dose, and duration of administration)	
	Diet	**Co-intervention**
Elemental nutrition + infliximab group	Elemental nutrition (1200–1500 mL) nasogastric tube infusion during night-time; Brand: Elental (Ajinomoto, Tokyo); One Elental pack contained 80 g of powdered ED, which is to be dissolved in warm water to give 300 mL of solution before administration. The calorie density 1 kcal/mL Duration: 56 wks (14 mo) Restricted diet - low fat (20–30 g/day) diet during daytime according to instructions to take 35–40 kcal/kg ideal body weight daily Infliximab (5 mg/kg, every 8 weeks)	Mesalazine (Pentasa 3 g/day), Azathioprine (Imuran 50–100 mg/day)
Infliximab group	Infliximab (5 mg/kg, every 8 weeks) Unrestricted diet	Mesalazine (Pentasa 3 g/day), Azathioprine (Imuran 50–100 mg/day)
Intervention 3 group	NA	NA

Patient baseline characteristics			
	Elemental nutrition + infliximab group	**Infliximab group**	**Intervention 3 group**
Age (years) Mean (SD)	31.0 (9.0)	33.0 (7.8)	NA
Sex –female n/N (%)	12/32 (37.5)	8/24 (33.3)	NA
Weight (kg) Mean (SD)	NR	NR	NA
BMI (kg/m^2) Mean (SD)	NR	NR	NA
Smoking n/N (%)	4/32 (12.5)	4/24 (16.6)	NA
Previous bowel resection n/N (%)	11/32 (34.4)	8/24 (33.3)	NA
Duration of CD (months) Mean (SD)	33.0 (24.8)	35.0 (19.6)	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	102.1 (18.1)	102.3 (22.5)	NA
Crohn's Disease Endoscopic Index of Severity (CDEIS) Mean (SD)	NR	NR	NA
Disease activity other than CDAI (specify)	NR	NR	NA
Mucosal ulceration n/N (%)	NR	NR	NA

Other complications n/N (%)	NR	NR		NA
Efficacy outcomes				
For each timing of assessment please provide a separate table *For scores, extract only total scores* Post-baseline follow-up assessment timing (Specify): 56 wks (14 mo)				
	Elemental nutrition + infliximab group	**Infliximab group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Patients remaining in remission n/N (%)	25/32 (78.1)	16/24 (66.6)	NA	p=0.51 (NS) study reported RR=1.17 (0.83, 1.64) calculated
Duration of remission (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Risk of relapse or recurrence n/N (%)	7/32 (21.8)	8/24 (33.3)	NA	p=0.51 (NS) study reported RR=0.65 (0.27, 1.56) calculated
Time to relapse (months) Mean (SD) or 95% CI	NR	NR	NA	NA
Survival rate (% patients in remission who have not relapsed) (Kaplan-Meier estimate and 95% CI)	NR	NR	NA	p=0.32 (NS)
Patients achieving mucosal healing n/N (%)	NR	NR	NA	NA
Crohn's Disease Activity Index (CDAI) Mean (SD)	NR	NR	NA	p>0.05 (NS)
The Short Form Health Survey (SF-36) Mean (SD) 95% CI	NR	NR	NA	NA
The Short Form Health Survey (SF-12) Mean (SD) 95% CI	NR	NR	NA	NA
The Euro-Qol questionnaire (EQ-5D) Mean (SD) 95% CI	NR	NR	NA	NA
Other HQOL (specify) Mean (SD) 95% CI	NR	NR	NA	NA

Weight (kg) Mean (SD) 95% CI	NR	NR	NA	NA
Weight gain (kg) Mean change (SD) 95% CI	NR	NR	NA	NA
Body mass index (kg/m^2) Mean change (SD) 95% CI	NR	NR	NA	NA
Height gain (cm) Mean (SD) 95% CI	NR	NR	NA	NA
Linear growth rate (mean height-for-age Z-score)	NR	NR	NA	NA
Adherence n/N (%)	25/32 (78.1)	NR	NA	NA
Need for surgery n/N (%)	NR	NR	NA	NA
Steroid dose tapering n/N (%)	NR	NR	NA	NA
Withdrawal from steroids n/N (%)	NR	NR	NA	NA
Adverse events due to treatment n/N (%)	NR	NR	NA	NA

Complications - Number (%) of patients with an event [if more than one follow-up, choose and specify the last follow up]				
	Elemental nutrition + infliximab group	**Infliximab group**	**Intervention 3 group**	**Between-group difference p value (or 95% CI)***
Impaired growth n/N (%)	NR	NR	NA	NA
Delay in pubertal development n/N (%)	NR	NR	NA	NA
Bowel obstruction	NR	NR	NA	NA
Fistulae	NR	NR	NA	NA
Abscess	NR	NR	NA	NA
Colon/bowel cancer	NR	NR	NA	NA
Intestinal infection	NR	NR	NA	NA
Others (Specify)	NR	NR	NA	NA

Authors conclusion
After 56 wks of follow-up, the effect of addition of elemental nutrition to infliximab was not statistically significant for the maintenance of remission rate and CDAI scores
Reviewer's conclusion
Assignment depended on compliance, i.e., pts with good compliance were assigned to elemental nutrition group and those with low compliance to infliximab alone group. The maintenance rates of clinical remission and CDAI scores were not significantly different between the elemental nutrition and control groups after 56 weeks of follow-up; age and gender did not significantly modify the observed effect of elemental nutrition on the maintenance of remission rates

* Risk ratio, risk difference, or mean difference (specify if it is between mean change values from baseline; or between mean final end-point values)

8.4 Appendix IV: The risk of bias assessment of included primary study reports

RCTs

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Hanai 2012[50]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	Random sequence generation		Group assignment was done by a random process	Low ROB
	Allocation concealment		No information provided	Unclear ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	No information provided, but probably not blinded; their knowledge of the treatment likely to influence the outcome reporting	High ROB
		Objective (e.g., radiography, endoscopy)	Although participants and personnel not blinded, their knowledge of the treatment unlikely to influence the outcome reporting	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	No information provided, but even if blinded, the reporting of subjective outcomes may have already been influenced	High ROB
		Objective (e.g., radiography, endoscopy)	Even if not blinded, the assessment of objective outcomes unlikely to be influenced	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	Although there were 11 withdrawals, the assessed data was complete (no missing outcomes)	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	Although there were 11 withdrawals, the assessed data was complete (no missing outcomes)	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		Cumulative probability (survival) of maintaining remission incompletely reported (only p values)	High ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP], baseline imbalance in important characteristics		No serious issues detected (funding source not reported, statistical methods adequate, no major baseline imbalance across the study groups	Low ROB
ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias				

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	Maintenance of remission (CDAI<150): High ROB
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Occurrence of relapse/recurrence (CDAI ≥200 or the need for an additional medication to suppress worsening symptoms), need for surgery, adverse events: Low ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias	

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Takagi 2006,[52, 53] Takagi2009[54]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	Random sequence generation		A block randomisation (block size of 10) was made with a random number table	Low ROB
	Allocation concealment		Randomised allocation done independently of the two clinical centres by the randomisation centre.	Low ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	Participants and personnel not blinded; their knowledge of the treatment likely to influence the reporting of outcome	High ROB
		Objective (e.g., radiography, endoscopy)	Although participants and personnel not blinded, their knowledge of the treatment unlikely to influence the reporting of outcome	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	Blinded (see below), but subjective outcomes may have been already influenced since patients and personnel were not blinded	High ROB
		Objective (e.g., radiography, endoscopy)	To blind the principal investigators at each site, the results (lab tests, CDAI) were reviewed by co-investigators who had no contact with patients, and these results were reported in a separate case report form	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	No missing outcome data	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	No missing outcome data	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		Remission rates not reported	High ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP], baseline imbalance in important characteristics		No serious issues detected (i.e., no external funding received, statistical methods adequate, ITT analysis, no major baseline imbalance between the study groups)	Low ROB
ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias				

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	Quality of life measure (IBDQ): High ROB
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Occurrence of relapse/recurrence (CDAI > 200, or the need for therapy to induce remission), adherence, adverse events: Low ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias; IBDQ= Inflammatory Bowel Disease Questionnaire	

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Verma 2001[55]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	Random sequence generation		No information provided	Unclear ROB
	Allocation concealment		No information provided	Unclear ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	No information provided, but probably not blinded; their knowledge of the treatment likely to influence the outcome reporting	High ROB
		Objective (e.g., radiography, endoscopy)	Although participants and personnel not blinded, their knowledge of the treatment would not influence the outcome reporting	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	No information provided, but even if blinded, the reporting of subjective outcomes may have already been influenced	High ROB
		Objective (e.g., radiography, endoscopy)	No information provided, but even if not blinded the assessment of objective outcomes unlikely to be influenced	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	Although there were 6 (18%) withdrawals, the analysed data was complete (no missing outcome)	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	Although there were 6 (18%) withdrawals, the analysed data was complete (no missing outcome)	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		Outcomes were not pre-specified in Methods section, only in the abstract; need for surgery was not reported in Results section; selective reporting likely	High ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP], baseline imbalance in important characteristics		No funding reported; statistical analyses adequate; there was some imbalance in the elemental nutrition group being on steroids for shorter period, higher CDAI, and lower weight than the control group	Unclear ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; ROB=risk of bias

* Statement, description or quote supporting the judgment

** Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	Occurrence of relapse/recurrence (CDAI ≥200 or increased by 100 points from baseline): High ROB
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Maintenance of remission (absence of diarrhoea and abdominal pain, CDAI≤150 in the 2 weeks preceding the study, and ESR<20 mm/h), withdrawal from steroids, adherence: Unclear ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias	

Non-RCTs

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Hirakawa 1993[51]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)		There was some imbalance in induction therapy and distribution of lesion across the study groups	High ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	Pure subjective outcomes: NR No information on blinding but probably not blinded	NA
		Objective (e.g., radiography, endoscopy)	No information on blinding but probably not blinded. However, given the objective outcomes their knowledge of the treatment would not influence the outcome reporting	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	Pure subjective outcomes: NR No information on blinding but probably not blinded	NA
		Objective (e.g., radiography, endoscopy)	No information on blinding but probably not blinded. However, given the objective outcomes their knowledge of the treatment would not influence the outcome reporting	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	Pure subjective outcomes: NR	NA
		Objective outcomes (e.g., radiography, endoscopy)	8 patients were excluded from the analyses (incomplete outcome data)	High ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		The analyses for survival of remission, remission maintenance rates, and relapse rates were incompletely reported (no or partial numerical data)	High ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]		Funding source not stated, PP analysis instead of ITT, possible imbalance in unmeasured prognostic factors	High ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias

[*] Statement, description or quote supporting the judgment
[**] Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	NR (see below): NA
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Maintenance of remission (cumulative survival): High ROB Adherence: Low ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias; IOIBD= International Organization for the Study of Inflammatory Bowel Disease: ESR=erythrocyte sedimentation rate; CRP=C-reactive protein	

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Verma 2000[56]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)		The elemental nutrition group had shorter disease duration (60.3 vs. 91.0 months), greater ESR, and longer steroid use compared to control group	High ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	No information on blinding but probably not blinded; their knowledge of the treatment likely to influence the outcome reporting	High ROB
		Objective (e.g., radiography, endoscopy)	No information on blinding but probably not blinded. However, given the objective outcomes their knowledge of the treatment would not influence the outcome reporting	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	No information on blinding; the reporting of subjective outcomes may have already been influenced	High ROB
		Objective (e.g., radiography, endoscopy)	No information on blinding; however, given the objective outcomes their knowledge of the treatment would not influence the outcome reporting	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	Complete data analysed	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	Complete data analysed	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		No pre-specification of outcomes (Methods section)	High ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]		No funder reported; statistical analyses adequate; ITT used	Low ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	Maintenance of remission (CDAI<150), CDAI score: High ROB
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Occurrence of relapse/recurrence (increase in CDAI by >100 points since baseline or final CDAI >150 points; need of surgery; increased doses of steroids), time to relapse, adherence, steroid dose tapering, withdrawal from steroids, adverse events: Unclear ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias	

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Yamamoto 2007a[30, 59, 60]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)		No major imbalance between the study groups in the pre-specified important prognostic factors. However, patients with good compliance were assigned to elemental nutrition group and those with low compliance to no treatment group; this selective assignment may have generated differences between the groups in not otherwise pre-specified factors	Unclear ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	Not blinded; subjective, i.e., patient-reported outcomes reporting likely influenced	High ROB
		Objective (e.g., radiography, endoscopy)	Not blinded; objective outcomes reporting unlikely to be influenced	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	No information; regardless of blinding status, subjective, i.e., patient-reported outcomes reporting likely influenced	High ROB
		Objective (e.g., radiography, endoscopy)	Endoscopic investigators were blind to patient status; objective outcomes assessment unlikely to be influenced	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	Outcomes for all patients available (complete data analysed)	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	Outcomes for all patients available (complete data analysed)	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		Main outcomes pre-specified (Methods section) and reported	Low ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]		No external funding received; statistical methods adequate; ITT analysis done	Low ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	Maintenance of remission (CDAI<150), occurrence of relapse/recurrence (CDAI≥150, CDAI≥200): High ROB
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Occurrence of relapse/recurrence (Rutgeerts score≥2), adherence, need for surgery: Low ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias	

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Yamamoto 2007b[57]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)		No major imbalance between the study groups in the pre-specified important prognostic factors. However, patients with good compliance were assigned to elemental nutrition group and those with low compliance to no treatment group; this selective assignment may have generated differences between the groups in not otherwise pre-specified factors	Unclear ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	Not blinded; the knowledge of the treatment could have influenced the outcome recording	High ROB
		Objective (e.g., radiography, endoscopy)	Not blinded; the knowledge of the treatment would not have influenced the outcome recording	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	Lab investigators were blinded to the clinical data; however the collected patient-reported outcome data may have already been influenced	High ROB
		Objective (e.g., radiography, endoscopy)	Lab investigators were blinded to the clinical data; the blinding status unlikely to influence the outcome assessment	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	Outcome data for all patients was available	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	Outcome data for all patients was available	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		All pre-specified outcome (Methods) were reported (Results)	Low ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]		No funding reported; analyses were adequate; ITT analysis done	Low ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	Maintenance of remission (CDAI<150), occurrence of relapse/recurrence (CDAI≥150), CDAI score: High ROB
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Mucosal healing (endoscopic remission), weight, BMI, adherence, need for surgery: Low ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias	

Name of first reviewer: Alexander Tsertsvadze
Name of second reviewer: Paul Sutcliffe
First author surname year of publication: Yamamoto 2010[58]

Bias domain	Source of bias		Support for judgment*	Authors' judgment**
Selection bias	The presence/absence of baseline between-group imbalance in important prognostic characteristics/factors (e.g., age, sex, CDAI, duration of CD, location of CD, complications during induction therapy, type of induction therapy, pre-study compliance, co-intervention, and/or smoking)		No major imbalance between the study groups in the pre-specified important prognostic factors. However, patients with good compliance were assigned to elemental nutrition group and those with low compliance to infliximab alone group; this selective assignment may have generated differences between the groups in not otherwise pre-specified factors	Unclear ROB
Performance bias	Blinding of participants and Personnel	Subjective (e.g., patient-reported)	No information provided, but probably not blinded; their knowledge of the treatment likely to influence the outcome reporting	High ROB
		Objective (e.g., radiography, endoscopy)	Although participants and personnel not blinded, their knowledge of the treatment would not influence the outcome reporting	Low ROB
Detection bias	Blinding of outcome assessors	Subjective (e.g., patient-reported)	No information provided, but even if blinded, the reporting of subjective outcomes may have already been influenced	High ROB
		Objective (e.g., radiography, endoscopy)	No information provided, but even if not blinded the assessment of objective outcomes unlikely to be influenced	Low ROB
Attrition bias	Incomplete outcome data	Subjective outcomes (e.g., patient-reported)	The analysed data was complete (no missing outcome)	Low ROB
		Objective outcomes (e.g., radiography, endoscopy)	The analysed data was complete (no missing outcome)	Low ROB
Reporting bias	Selective reporting of the outcome, subgroups, or analysis		All pre-specified (in Methods section) outcomes were reported (in Results section)	Low ROB
Other bias	Funding source, adequacy of statistical methods used, type of analysis [ITT/PP]		No funding reported; statistical analyses adequate; ITT analysis reported	Low ROB

ITT=intention to treat; PP=per protocol; NA=not applicable; CDAI=Crohn's disease activity index; ROB=risk of bias

* Statement, description or quote supporting the judgment
** Low risk of bias, high risk of bias, or unclear risk of bias

Summary assessment of the within-study risk of bias for an outcome across domains

Outcome measure	Summary risk of bias across all domains within a study
Subjective (list of outcomes): Maintenance of remission (e.g., CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), time to relapse/recurrence (e.g., CDAI≥150), quality of life measures, clinical scores of severity (e.g., CDAI)	Maintenance of remission (CDAI<150), occurrence of relapse/recurrence (e.g., CDAI≥150), clinical scores of severity (CDAI): High ROB
Objective (list of outcomes): Maintenance of remission (includes additional objective parameters besides clinical), occurrence of relapse/recurrence (includes additional objective parameters besides clinical), time to relapse/recurrence (includes additional objective parameters besides clinical), mucosal healing (endoscopic remission), weight gain, linear growth rate, complications, adverse events, adherence	Adherence: Low ROB
CD=Crohn's Disease; CDAI= Crohn's Disease Activity Index; ROB=risk of bias	

8.5 Appendix V: Studies excluded with reasons

N	Study	Reason for exclusion
1	Belli DC, Seidman E, Bouthillier L, Weber AM, Roy CC, Pletincx M, *et al.* Chronic intermittent elemental diet improves growth failure in children with Crohn's disease. *Gastroenterology*. 1988;**94**(3):603-10	<80% participants in remission
2	Cucchiara S, Guandalini S, Staiano A, Ferola A, Romaniello G, Latte F, et al. Remission of colonic crohns-disease induced by elemental diet. *Italian Journal of Gastroenterology*. 1984;**16**(4):302-4	Case report
3	Esaki M, Matsumoto T, Hizawa K, Nakamura S, Jo Y, Mibu R, et al. Preventive effect of nutritional therapy against postoperative recurrence of Crohn disease, with reference to findings determined by intra-operative enteroscopy. *Scandinavian Journal of Gastroenterology*. 2005;**40**(12):1431-7	Unclear control group
4	Fukuda Y, Okui M, Tamura K, Shimoyama T. Serum fatty acid and disease activity in Crohn's disease patients during maintenance therapy with elemental diet. 1999 [cited; Available from: http://0-onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/882/CN-00382882/frame.html]	Irrelevant treatment/outcome
5	Geerling BJ, Badart-Smook A, van Deursen C, van Houwelingen AC, Russel M, Stockbrugger RW, et al. Nutritional supplementation with n-3 fatty acids and antioxidants in patients with Crohn's disease in remission: Effects on antioxidant status and fatty acid profile. *Inflammatory Bowel Diseases*. 2000;**6**(2):77-84	Irrelevant treatment/outcome
6	Gorard DA, Hunt JB, Paynejames JJ, Palmer KR, Kumar PJ, Clark ML, et al. Relapse rates in Crohns-disease after initial treatment with elemental diet or prednisolone. *Gut.* 1991;**32**(5):A582	Abstract
7	Harries AD, Jones LA, Danis V, Fifield R, Heatley RV, Newcombe RG, et al. Controlled trial of supplemented oral nutrition in Crohn's disease. *Lancet*. 1983;**1**(8330):887-90	Participants with active CD
8	Herzog D, Deslandres C, Martin S, Rasquin A, Alvarez F, Bouthillier L, et al. Cyclical exclusive semi-elemental diet therapy normalizes growth and decreases relapse rate in pediatric Crohn's disease. *Gastroenterology*. 1997;**112**(4):A995	Abstract
9	Hunt JB, Payne-James JJ. A randomised controlled trial of elemental diet versus prednisolone in treatment of new and recurrent Crohn's disease. 1989 [cited; Available from: http://0-onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/761/CN-00258761/frame.html]	Abstract
10	Hunt JB, Payne-James JJ, Palmer KR, Kumar PK, Clark ML, Farthing MJ, et al. A	Abstract

	randomised controlled trial of elemental diet versus prednisolone in the treatment of new & recurrent Crohns disease. 1989 [cited; Available from: http://0-onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/382/CN-00281382/frame.html]	
11	Imes S, Pinchbeck B, Dinwoodie A, Walker K, Thomson AB. Effect of Ensure, a defined formula diet, in patients with Crohn's disease. *Digestion*. 1986;**35**(3):158-69.	Participants with active CD
12	Kamata N, Watanabe K, Tsukahara T, Hagihara Y, Morimoto K, Noguchi A, et al. Concomitant elemental diet therapy is effective in sustaining infliximab scheduled maintenance therapy in patients with crohn's disease to prevent loss of response. *Gastroenterology*. 2013;**1**:S433	Abstract
13	Matsui T, Ueki M, Yamada M, Sakurai T, Yao T. Indications and options of nutritional treatment for Crohn's disease. A comparison of elemental and polymeric diets. 1995 [cited; Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/053/CN-00123053/frame.html]	Abstracts of 3 studies
14	Otley AR, Murray A, Christensen B, Williams T, Ste-Marie M, Rashid M. Primary enteral nutrition therapy induces and maintains remission, and reduces steroid exposure in a pediatric Crohn's disease population. *Gastroenterology*. 2005;**128**(4):A584	Abstract
15	Papadopoulou A, Rawashdeh MO, Brown GA, McNeish AS, Booth IW. Remission following an elemental diet or prednisolone in Crohn's disease. *Acta Paediatrica, International Journal of Paediatrics*. 1995;**84**(1):79-83	Retrospective (cohort) study
16	Roggero P, Santus F, Barabino A, Canani RB, Cucchiara S, Guariso G, et al. A prospective pediatric multicenter trial of enteral nutrition and azathioprine in preventing relapses of Crohn disease: preliminary results. 2003 [cited; Available from: http://0-onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/329/CN-00593329/frame.html]	Abstract
17	Shoda R, Yamato S. Comparison of therapeutic efficacy of elemental and polymeric enteral numition in the patients with quiescent Crohn's disease: A pilot cross-over trial. *Gastroenterology*. 2007;**132**(4):A523	Abstract
18	Takahashi S, Takagi S, Shiga H, Umemura K, Endo K, Kakuta Y, et al. Scheduled maintenance therapy with infliximab improves the prognosis of Crohn's disease: a single center prospective cohort study in Japan. *Tohoku Journal of Experimental Medicine.* 2010;**220**(3):207-15	Retrospective (cohort) study
19	Vaisman N, Griffiths A, Pencharz PB. Comparison of nitrogen utilization of two elemental diets in patients with Crohn's disease. *J Pediatr Gastroenterol Nutr*. 1988;**7**(1):84-8	Unclear population/control group
20	Watanabe O, Ando T, Ishiguro K, Takahashi H, Ishikawa D, Miyake N, et al. Enteral	Retrospective

	nutrition decreases hospitalization rate in patients with Crohn's disease. *Journal of Gastroenterology and Hepatology*. 2010;**25**(SUPPL. 1):S134-S7	(cohort) study
21	Wierdsma NJ, Van Bodegraven AA, Uitdehaag BMJ, Arjaans W, Savelkoul PHM, Kruizenga HM, et al. Fructo-oligosaccharides and fibre in enteral nutrition has a beneficial influence on microbiota and gastrointestinal quality of life. *Scandinavian Journal of Gastroenterology*. 2009;**44**(7):804-12	Head and neck cancer pts
22	Woolner JT, Parker TJ, Kirby GA, Hunter JO. The development and evaluation of a diet for maintaining remission in Crohn's disease. *Journal of Human Nutrition and Dietetics*. 1998;**11**(1):1-11	Irrelevant treatment/outcome
23	Yamamoto T, Shiraki M. Efficacy of enteral nutrition during infliximab maintenance therapy in patients with Crohn's disease. *Digestive Diseases and Sciences*. 2013;**58**(6):1802-3	Comment
24	Yoshida K, Fukunaga K, Ikeuchi H, Kamikozuru K, Yokoyama Y, Hida N, et al. Infliximab mono-therapy prevented post operative recurrence of Crohn's disease after intestinal resection: A prospective randomized open trial in Japanese population. *Gastroenterology*. 2010;**1**:S691	Abstract